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PREPARATION AND REACTIONS OF ISOFLAVONE HETEROANALOGS. (A REVIEW)

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Methods for preparation of 3-hetarylchromones, which are isoflavone heteroanalogs, and the reactions of these compounds with either preservation or opening of the pyrone ring are reviewed.

The 4H-[1]-benzo-4-pyranone (chromone) system is the basis of the chemical structure of a large group of biologically active natural products known as flavonoids and isoflavonoids. Replacement of the aryl residue in isoflavonoids by hetaryl residue leads to compounds having a broad range of biological activity arising from the combination of chromone and heterocyclic residues in a single molecule. Thus, 3-hetarylchromones, which have been termed isoflavonoid heteroanalogs, display strong antiallergenic [1-12], anticholesterol [13, 14], hypolipedimic [15, 16], antimicrobial [17, 18], anti-inflammatory [19], fungicidal [18], and antiblastic activity [20, 21] and are central nervous system stimulators [19, 22-25].

1. METHODS OF SYNTHESIS OF 3-HETARYLCHROMONES

Two major approaches have been developed for the synthesis of hetarylchromones. The first approach involves construction of the chromone system from substituted α-hetaryl-2-hydroxyacetophenones, often using reagents such as ethoxalyl chloride, orthoformic ester, and acid anhydrides. The second method entails addition of the heterocycle to the prepared chromone system.

The two approaches are examined in detail. Methods for the preparation of some starting substituted α-hetarylacetophenones are also given in Section 1.1. Examples of the synthesis of chromones containing completely or partially hydrogenated heterocyclic substituents are given in Section 1.2 (in light of their potential ability for conversion into 3-hetarylchromones by means of aromatization).

1.1. Preparation of 3-hetarylchromones by construction of the chromone system

Thienyl derivatives I—III have been obtained by cyclization of α-(2-thienyl)-2,4,6-trihydroxyacetophenone using ethoxalyl chloride [26]:

Taras Shevchenko Kiev University, 252033 Kiev, Ukraine. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 3-23, January, 1999; Original article submitted June 3, 1997; revision submitted October 9, 1998.

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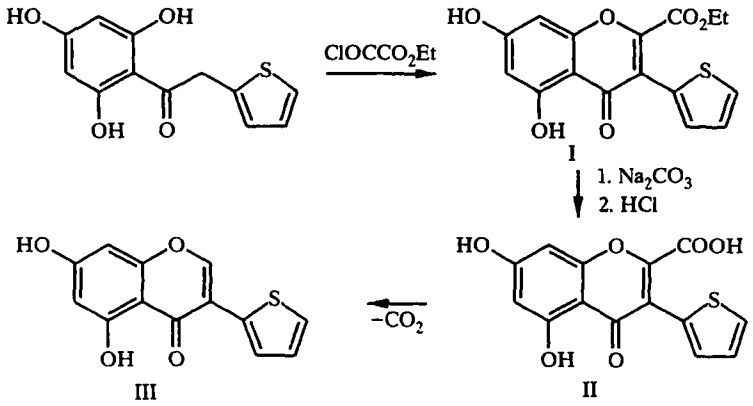
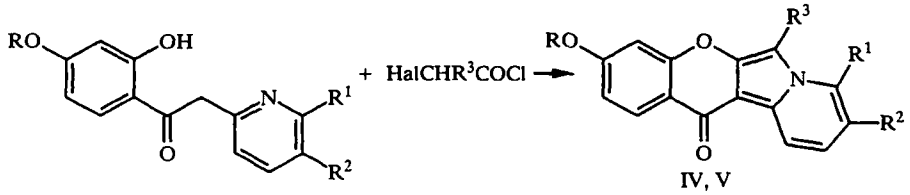
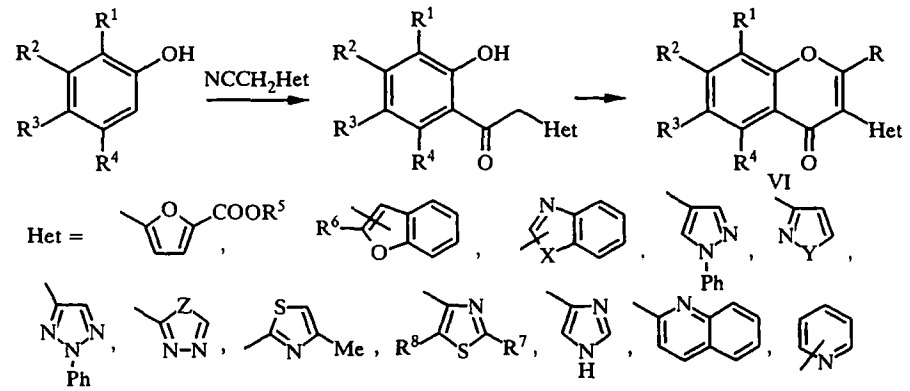


We should note that cyclization at the nitrogen atom of the hetaryl substituent also occurs in the reaction of substituted α-(2-quinolyl)acetophenones (see below, R^1R^2 = CH=CH—CH=CH) or α-(2-pyridyl)acetophenones ($R^1 = R^2 = H$) with α-haloacid chlorides to give 12H-chromeno-[3′,2′-3,4]pyrrolo[1,2-*a*]quinolin-12-ones (IV) [27] and 12H-chromeno-[2,3-*c*]indolizin-12-ones (V) [28], respectively.



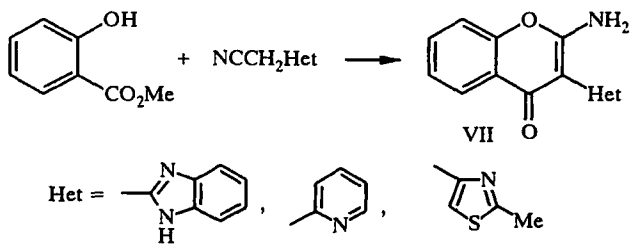
R = H, COMe, Me, C_3H_7; $R^1 = R^2 = H$, R^1R^2 = CH=CH—CH=CH;
R^3 = H, Me; Hal = Cl, Br

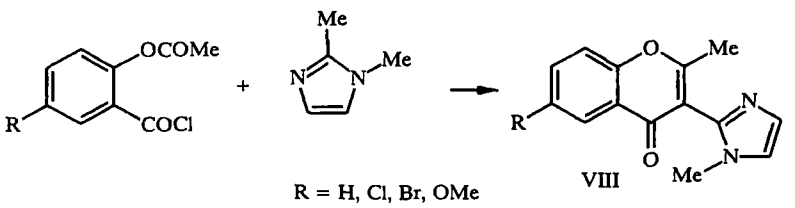
The condensation of phenols with various α-hetarylacetonitriles under conditions of the Hesh reaction and its modification with subsequent cyclization of the ketones obtained using such reagents as triethyl orthoformate, ethoxalyl chloride, trifluoroacetic anhydride, acetic anhydride, and acetic—formic anhydride gives furan and benzofuran [17, 29-38], benzothiazole [39-41], benzimidazole [17, 39, 42-44], pyrazole, thiadiazole [51], thiazole [16, 20, 21, 35-38, 52-62], imidazole [35, 63], quinoline [35, 36, 64, 65], and pyridine [18, 35, 36, 66] analogs VI of natural isoflavones. 3-(2-Pyridyl)chromone N-oxide was obtained under similar conditions from α-(2-pyridyl)-2-hydroxyacetophenone N-oxide and triethyl orthoformate [67].



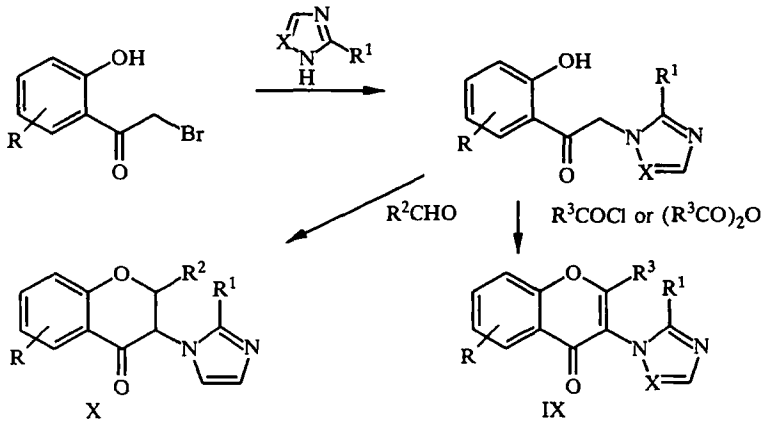
R = H, Me, CF_3, CO_2Et; R^1 = H, OH, Me; R^2 = H, OH, Me; R^3 = H, Alk, Cl;
R^4 = H, OH, Me; R^5 = Me, Et; R^6 = H, Me; R^7 = H, Me, Ph; R^8 = H, Me;
X = S, NH, N–Me, N–; Y = NH, O; Z = N–Ph, S

Hetarylchromones VII and VIII were synthesized in one step from salicylic acid derivatives and α-hetarylacetonitriles [68, 69] or dimethylimidazoles, respectively [70]:



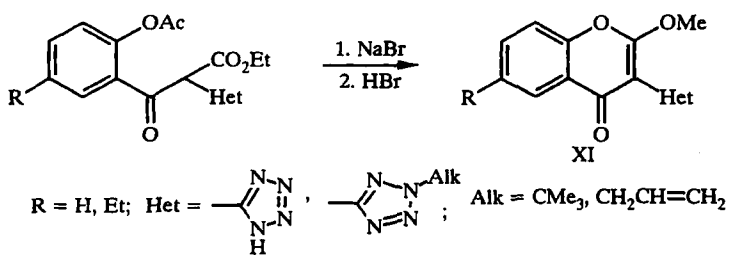


The reaction of phenacyl bromides with imidazole in DMF [13-15, 71-73] and also with imidazole or 1,2,4-triazole in acetonitrile with triethylamine [74] gave α-imidazolyl- and α-(1-triazolyl)acetophenones used for synthesis of the corresponding hetarylchromones IX and hetarylchromanones X.



R = H, OH, Alk, Cl, Br, COOH, OAlk; R^1 = H, Me; R^2 = H, Ar, Me;
R^3 = COOMe, Me, Ph; X = CH, N

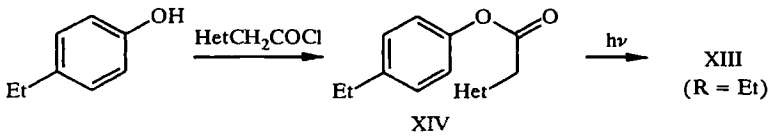
2-Methoxy-3-tetrazolylchromones XI were synthesized by the cyclization of 2-(2-*tert*-butyl-5-tetrazolyl)acetic acid ethyl ester by the action of HBr [75].



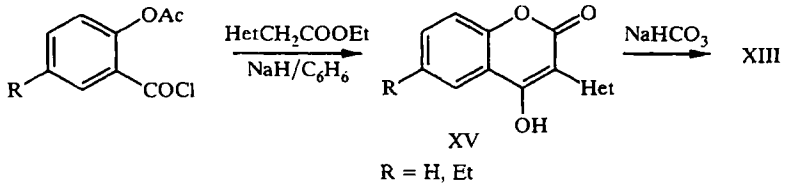
3-Tetrazolylchromones XII were also obtained through cyclization of α-(5-tetrazolyl)acetophenones XIII by the action of sodium ethylate and ethyl formate [76-79].

The following methods have been patented for the synthesis of starting compounds XIII in light of the strong antiallergenic activity of these chromones:

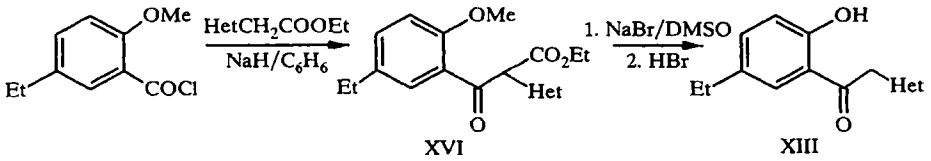
1) reaction of acetic acid derivatives with 4-ethylphenol and subsequent photorearrangement of the obtained esters XIV [76]:



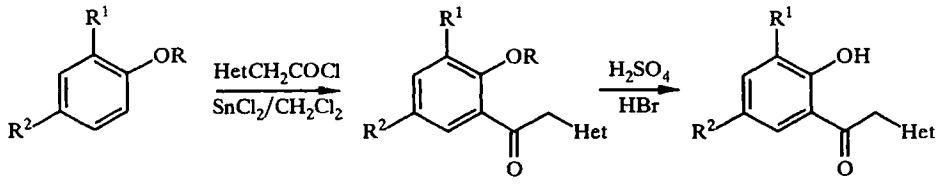
2) alkaline hydrolysis of 4-hydroxycoumarins XV obtained by interaction of ethyl tetrazolylacetate with 2-acetoxybenzoyl chloride in benzene under the action of sodium hydride [77]:



3) hydrolysis and decarboxylation of α-ethoxycarbonyl-2-methoxyacetophenone (XVI) obtained by acylation of ethyl tetrazolylacetate by 2-methoxy-5-ethylbenzoyl chloride in benzene under the action of sodium hydride [78]:

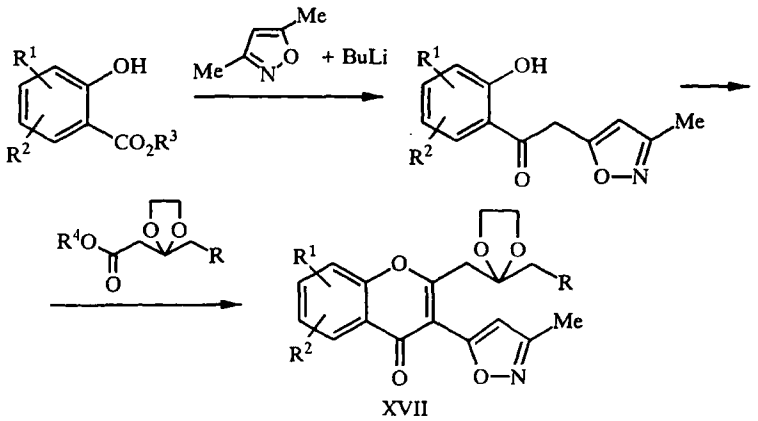


4) reaction of derivatives of α-tetrazolylacetyl chloride with phenols in methylene chloride in the presence of $SnCl_2$ [79]:



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

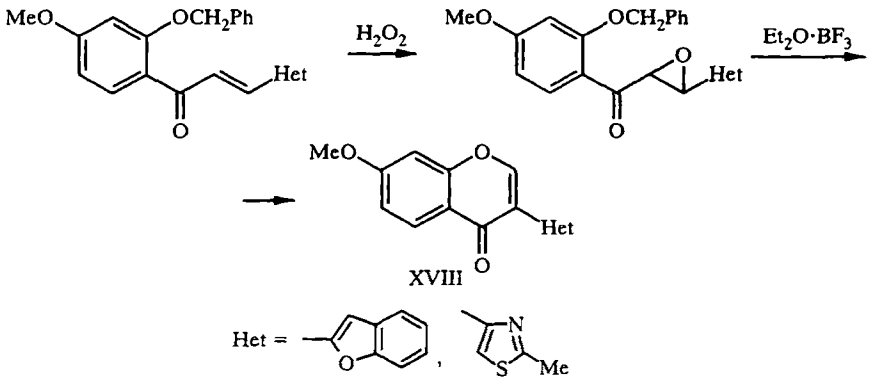
3-Isoxazolylchromones XVII were synthesized from derivatives of salicylic acid esters by condensation with 3,5-dimethylisoxazolyl anion and subsequent formation of the chromone system by reaction of the resultant substituted α-isoxazolylacetophenone with carboxylic acid derivatives [80]:



XVII

R = H, COOAlk; R^1, R^2 = Alk, OAlk; R^3 = not given ; R^4 = OH, Hal

A method has been developed to obtain 7-methoxy-3-hetarylchromones XVIII by the rearrangement of chalcone epoxides under the action of Lewis acids. The best yields of products were obtained by using boron trifluoride etherate [54, 81-83]:

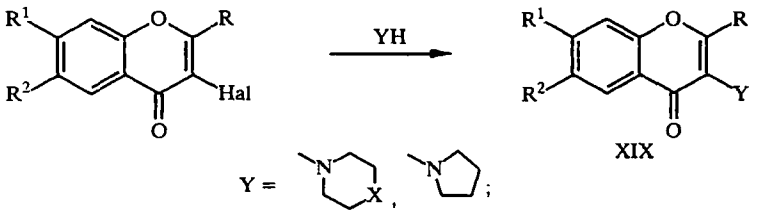


XVIII

Het =

1.2. Preparation of 3-hetarylchromones by fusion of a heterocyclic residue to the chromone system

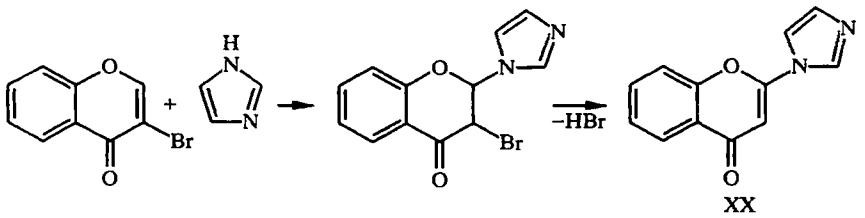
Amination of bromo- or 3-chlorochromones by heating these compounds with secondary cyclic amines such as pyrrolidine, piperidine, morpholine, and 1-methylpiperazine was used to obtain 3-hetarylchromones XIX, which are potential precursors of hetarylchromones containing C—N bond between the chromone system and nitrogen-containing heterocycle [22, 23, 84-87].



XIX

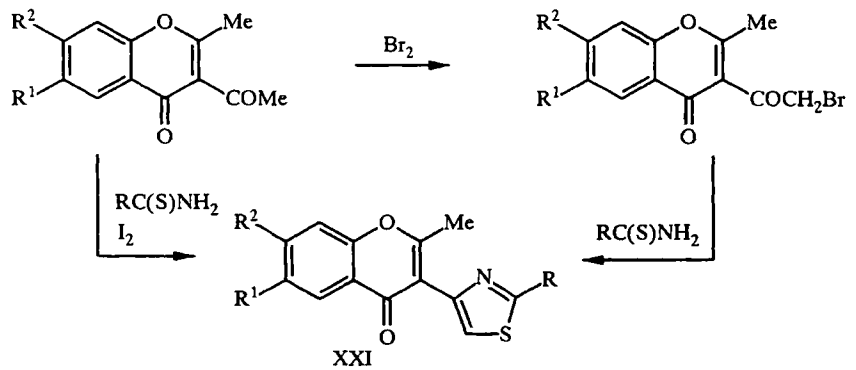
R = H, Me, Ph; R^1, R^2 = H, Cl, Me; X = CH_2, O, NMe; Hal = Cl, Br

The reaction of 3-bromochromone and imidazole has a different outcome. The Michael addition of imidazole leads to 2,3-dihydro-2-(1-imidazolyl)-3-bromochromanone, which undergoes dehydrobromination to give 2-(1-imidazolyl)chromone (XX) [72].



XX

The condensation of 2-methyl-3-bromoacetylchromones with acid thioamides and substituted thioureas in ethanol upon heating gives 3-(4-thiazolyl)chromones XXI, which are also formed directly upon heating of 2-methyl-3-acetylchromones and thioamides in the presence of iodine [19, 24, 25, 88].



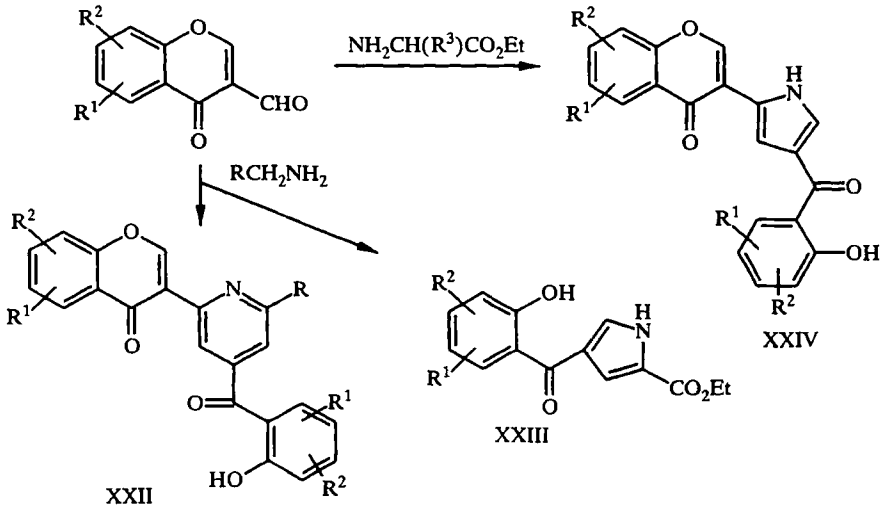
XXI

R = $-NH_2$, —NH—R^3, —R^4, —N X, —N N Me R^5 ; R^6

R^1, R^3 = H, Cl, Me; R^2 = H, Me; R^4 = H, Cl, NO_2;

R^5 = H, Me, Et; R^6 = Me,  ; X = NMe, NPh, O, CH_2; Y = O, S

Interest is found in the reaction of 3-formylchromones with glycine derivatives, which gives pyridine and pyrrole analogs of isoflavones [89, 90].



XXII

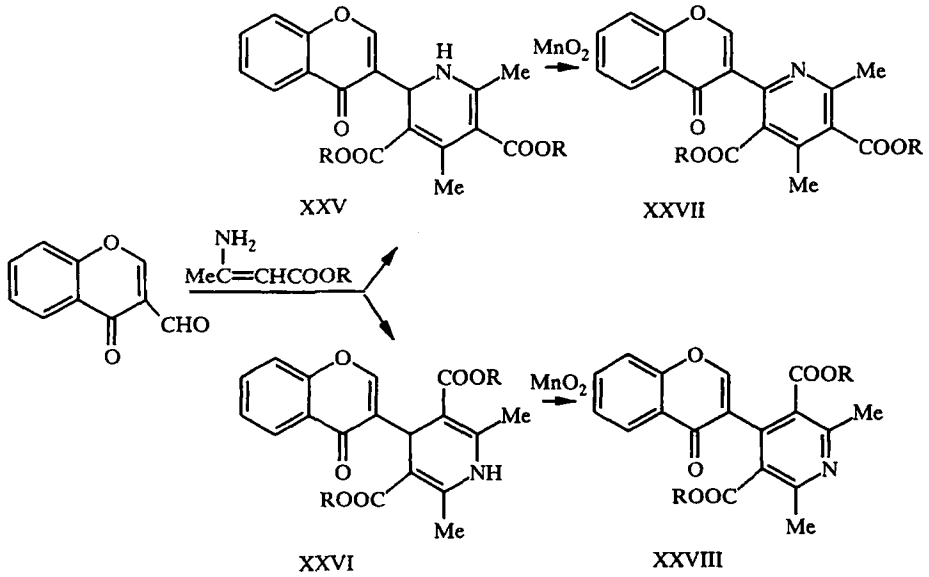
XXIII

XXIV

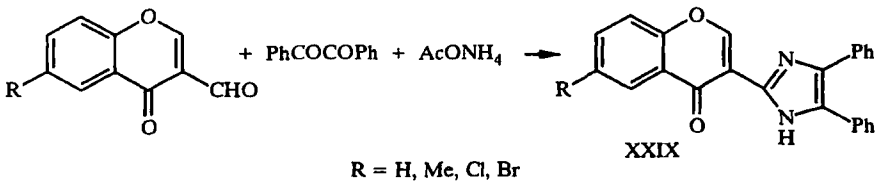
R = COOEt, CN; R^1, R^2 = H, Me, Cl, OMe, NO_2; R^3 = Me, Ph

Thus, a mixture of the corresponding 3-pyridylchromone XXII (R = RCO_2Et) and ethyl ester of 4-salicyloyl-2-pyrrolecarboxylic acid XXIII is obtained upon the action of ethyl ester of glycine on 3-formylchromones in the presence of catalytic amounts of *p*-toluenesulfonic acid in toluene at reflux. Products XXIII are formed when electron-donor or electron-withdrawing substituents are found at $C_{(6)}$ or $C_{(7)}$ in the chromone system. A substituent at $C_{(5)}$ in the chromone system facilitates formation of products XXII. The reaction of aminoacetonitrile with substituted 3-formylchromones leads exclusively to XXII (R = CN). 3-Pyrrolylchromones XXIV are formed in the case of ethyl α-methyl- or α-phenylaminoacetate. The structure of these products is independent on starting ester.

The Hantzsch reaction of 3-formylchromone with esters of β-aminocrotonic acid in acetic acid gives a mixture of substituted 3-(1,2-dihydro-2-pyridyl)- (XXV) and 3-(1,4-dihydro-4-pyridyl)chromones (XXVI), which were separated chromatographically and dehydrogenated to give the corresponding 3-pyridylchromones XXVII and XXVIII [91].

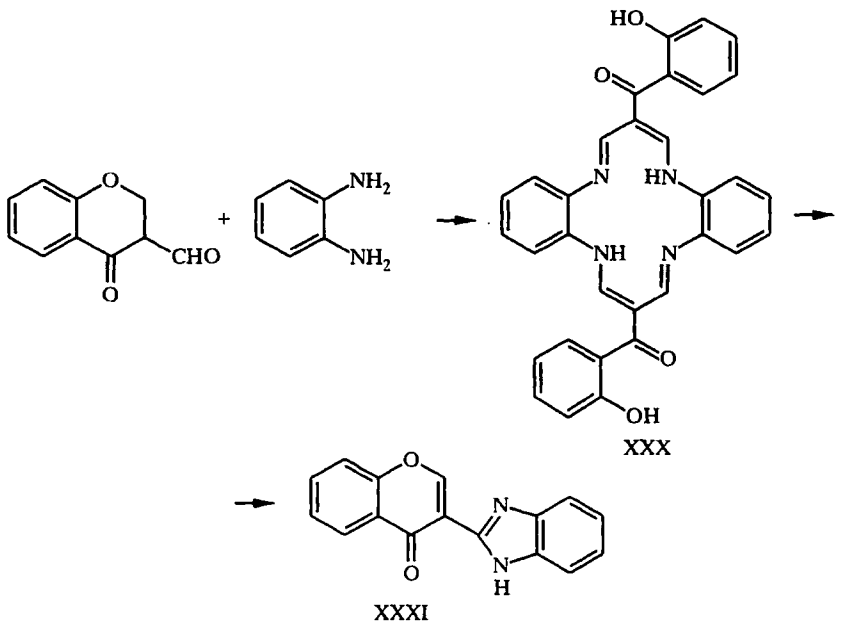


The reaction of 3-formylchromone and its derivatives with benzil and ammonium acetate in glacial acetic acid at reflux gives imidazolylchromones XXIX [92, 93]:



The analogous reaction with *o*-phenylenediamine proceeds to give a derivative of dibenzotetraazacyclotetradecatetraene (XXX), which is dehydrated to give 3-(2-benzimidazolyl)chromone (XXXI) [94].

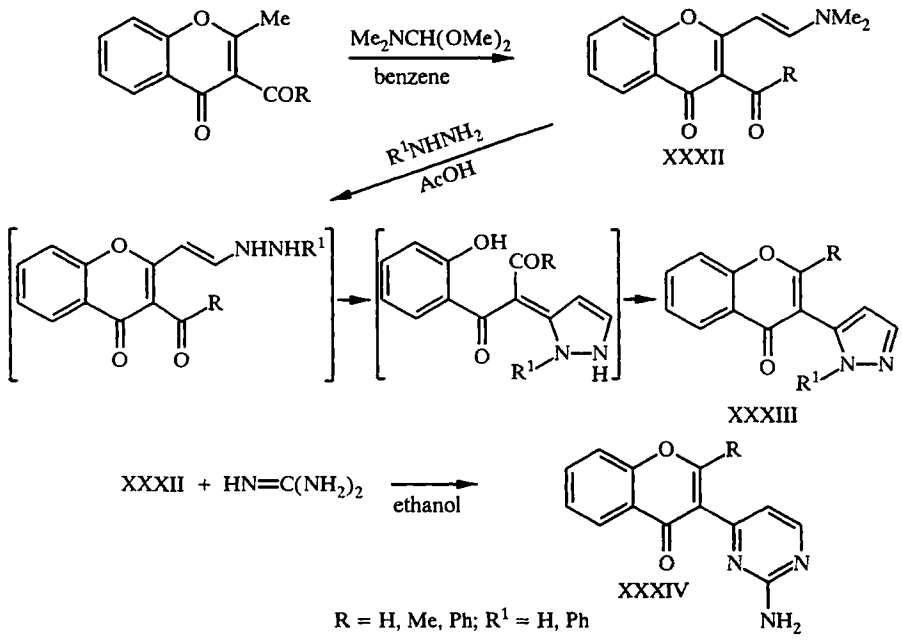
Heating of 2-methyl-3-acylchromones with dimethylaminodimethoxymethane in benzene at reflux gives aminovinylchromones XXXII. The dimethylaminomethyl group in XXXII is readily replaced by hydrazine or phenylhydrazine residue upon heating in acetic acid at reflux.



XXX

XXXI

Pyrazole analogs of isoflavones XXXIII are obtained by means of successive recyclizations of the reaction products [95, 96]. Heating of aminovinylchromones XXXII with guanidine in ethanol at reflux gives pyrimidine analogs of isoflavones XXXIV.



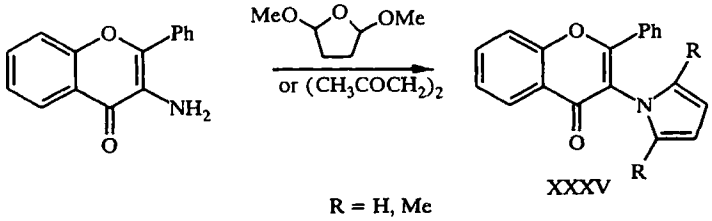
XXXII

XXXIII

XXXIV

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

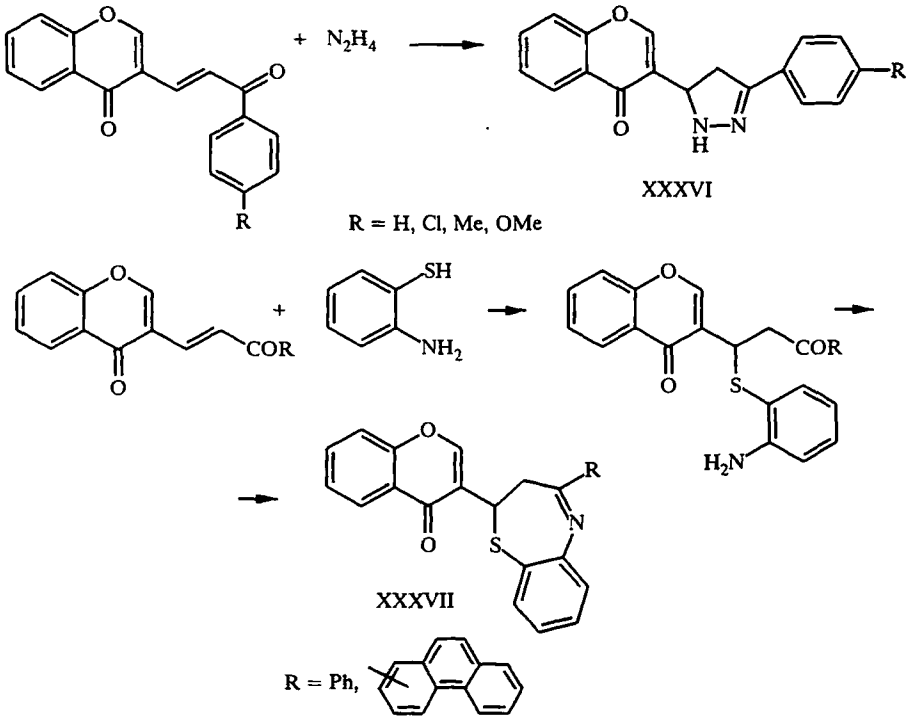
The reaction of 3-aminoflavone with 2,5-dimethoxytetrahydrofuran or 1,4-hexanedione in acetic anhydride gives pyrrole derivatives XXXV [97].



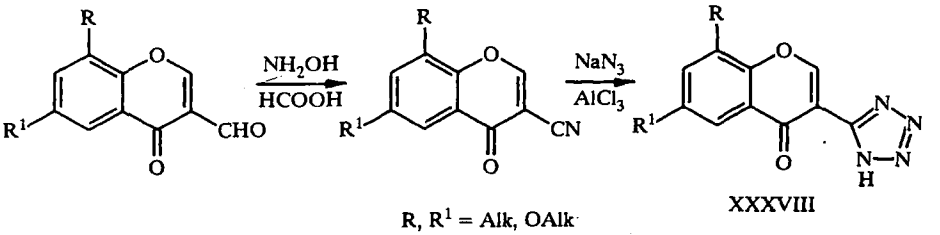
XXXV

R = H, Me

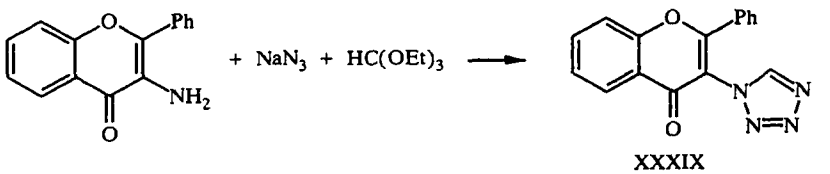
The reaction between 3-(2-acylvinyl)chromones and hydrazine in glacial acetic acid gives derivatives XXXVI containing pyrazoline ring [98], while the reaction of similar chromones with *o*-aminothiophenol and subsequent intramolecular cyclocondensation gives products XXXVII containing benzothioazepine residue [99].



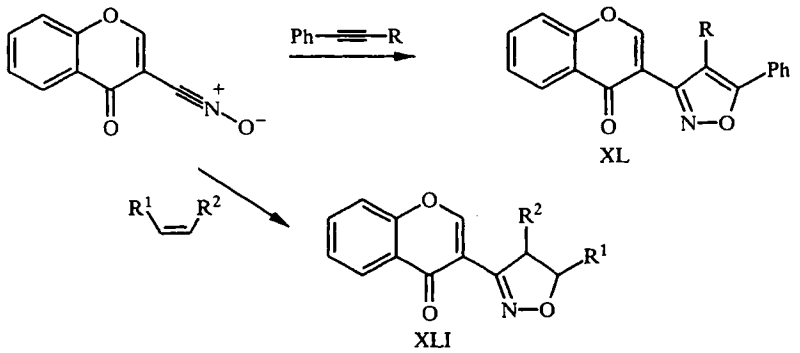
Methods have also been developed for the synthesis of 3-hetarylchromones using dipolar 1,3-cyclization. The reaction of 3-formylchromones with hydroxylamine hydrochloride in formic acid in the presence of sodium formate gives substituted 3-cyanochromones. The action of sodium azide on 3-cyanochromones in the presence of aluminium chloride in tetrahydrofuran gives 3-(5-tetrazolyl)chromones XXXVIII [1-12, 100].



The reaction of 3-aminoflavone with sodium azide and triethyl orthoformate gives 3-(1-tetrazolyl)-2-phenylchromone (XXXIX) [101]:



3-Chromonecarbonitrile N-oxide obtained from 3-formylchromone oxime by bromination with subsequent dehydrobromination reacts with phenylacetylenes to give 3-(3-isoxazolyl)chromones XL [102]. Isoxazoline derivatives XLI are obtained in the case of substituted ethylenes [103].

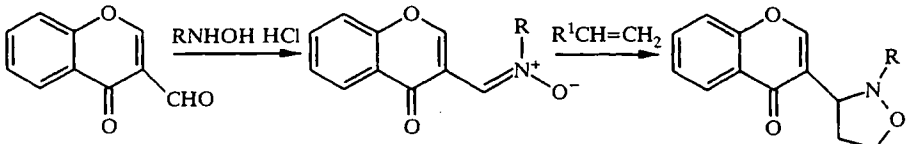


XL

XLI

R = H, Ph; R^1, R^2 = CN, Ph, CH_2Br, $C_6H_4CH_3$-*p*

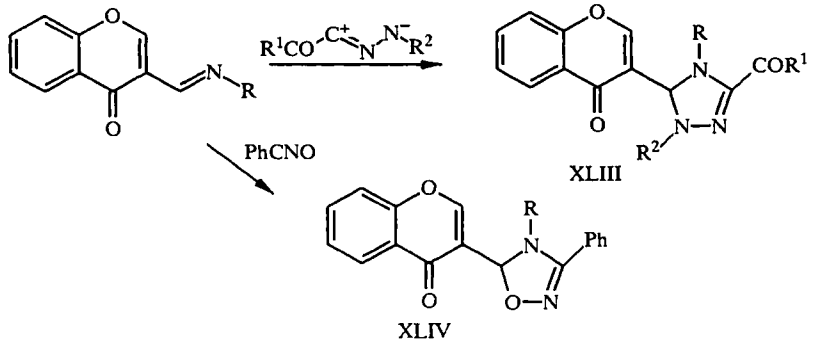
The reaction between 3-benzopyrancarbaldehyde and methylhydroxylamine hydrochloride or phenylhydroxylamine hydrochloride with subsequent addition to the intermediate alkene nitrones gives 3-isoxazolidinylchromones XLII [102].



R = Me, Ph; R^1 = CN, Ph, $C_6H_4CH_3$-*p*

XLII

The addition of imine oxides to Schiff bases gives substituted 3-triazolinylchromones XLIII [102], while the addition of benzonitrile oxides to Schiff bases gives oxadiazinylchromones XLIV [104].

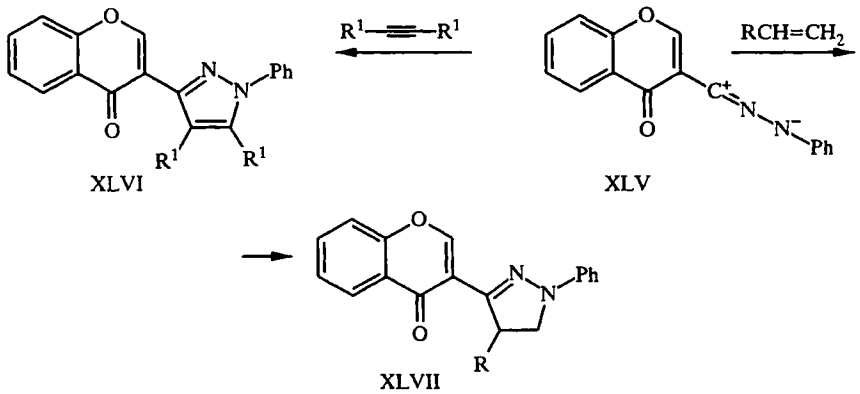


XLIII

XLIV

R = C_6H_4OMe-*p*, C_6H_4OEt-*p*; R^1 = Me, OEt; R^2 = C_6H_4Me-*p*, C_6H_4Br-*p*

In the same study [104] was also found that reaction of nitrilimines XLV with substituted acetylenes and ethylenes gives pyrazolylchromones XLVI and pyrazolinylchromones XLVII, respectively.

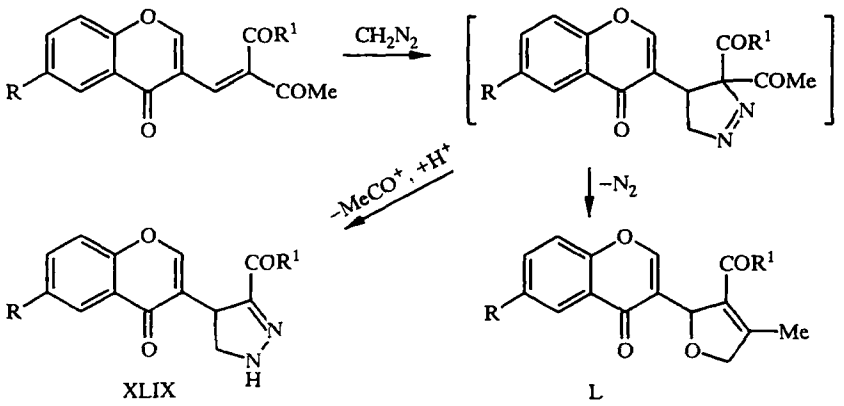


XLVI

XLV

XLVII

Treatment of 3-(2-diacylvinyl)chromones XLVIII with diazomethane and subsequent transformation of the resultant addition product gives pyrazolinylchromones XLIX as well as dihydrofuran analogs of isoflavones L [105].



XLIX L

R = H, Me, Cl; R^1 = Me, Ph

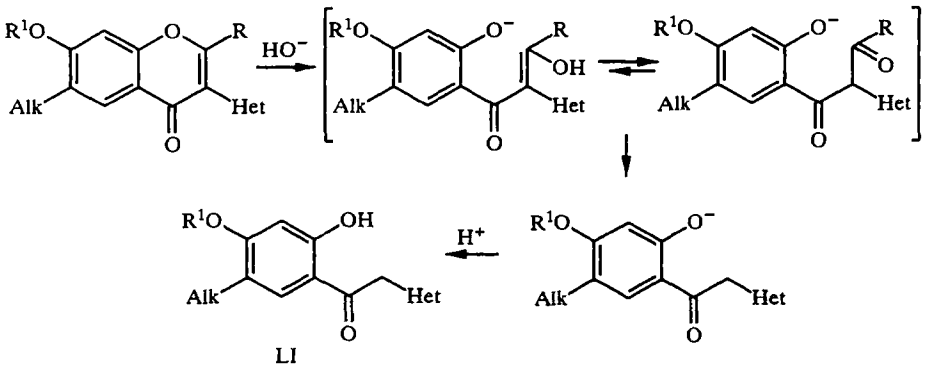
2. REACTIONS OF 3-HETARYLCHROMONES

Information on the chemical transformations of 3-hetarylchromones has been reviewed partially in the monograph [51]. We should note that, in contrast to the preparation of these compounds, their reactions have not been studied sufficiently.

The transformations of 3-hetarylchromones may occur with involvement of the chromone fragment or heterocyclic unit. Both opening and preservation of the pyrone ring is possible in the former case.

2.1. Action of alkali on 3-hetarylchromones

The reaction of chromones with alkali has long been used to determine the structure of these compounds. Thus, heating furan, benzofuran [106], thiazole [16, 20, 21, 53, 56], imidazole [70], and tetrazole analogs of isoflavones [75] with excess of alkali in aqueous ethanol leads to opening of the chromone ring and the resultant corresponding β-dicarbonyl derivative is converted into substituted α-hetarylacetophenone LI.



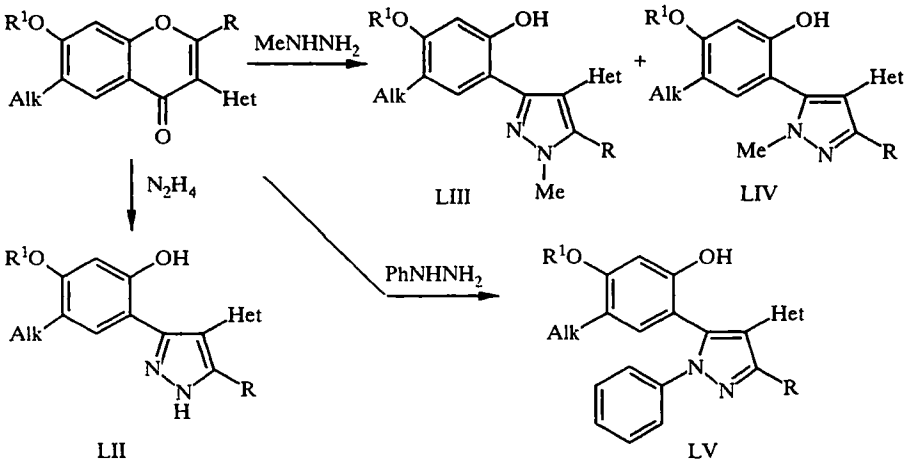
LI

R = H, Me, CF_3, OMe; R^1 = H, Me

The rate of this alkaline hydrolysis depends on the nature of substituent at $C_{(2)}$ of the chromone system. Thus, 3-hetarylchromones with electron-withdrawing substituents at this position and their unsaturated analogs undergo opening more rapidly than 2-methyl derivatives. When 7-OH group is present, the chromone system is much more resistant to the action of alkali.

2.2. Interaction with hydrazine and hydrazine derivatives

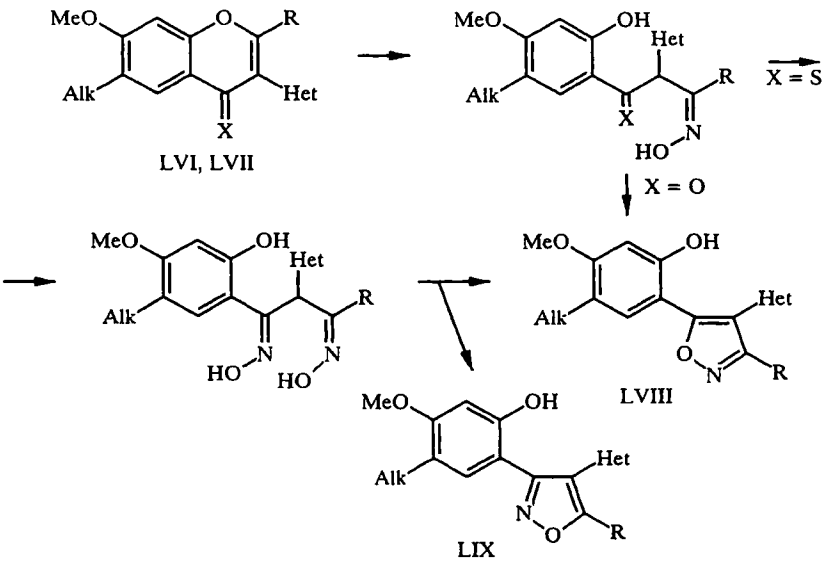
The reaction of 3-hetarylchromones containing furan and benzofuran [106-108], thiazole [16, 52-56, 109], benzothiazole [40, 41], benzimidazole [43], isoxazole [48], triazole [50], thiadiazole [51], imidazole [63], and quinoline residues [64] with hydrazine and its derivatives leads to opening of the chromone system and subsequent formation of pyrazole ring leading to the corresponding phenol derivatives LII—LV.



R = H, Me, CF_3; R^1 = H, Me

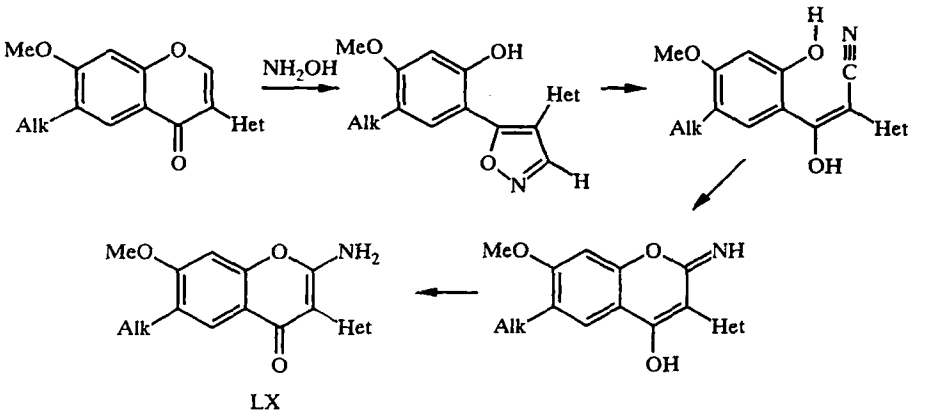
2.3. Reactions with hydroxylamine

The reactions of 3-hetarylchromones with hydroxylamine have been studied in detail in our previous works [106, 107]. Heating of hydroxylamine with 3-furyl-, 3-benzofuryl- [107, 108], 3-thiazolyl- [53, 56, 109], and 3-quinolylchromones LVI (X = O) or their thioxo analogs LVII (X = S) [64] in dry pyridine may give isoxazoles LVIII or LIX. In most cases, chromones LVI give isoxazoles LVIII, while thioxochromones LVII give a mixture of regioisomers LVIII and LIX [53, 64].



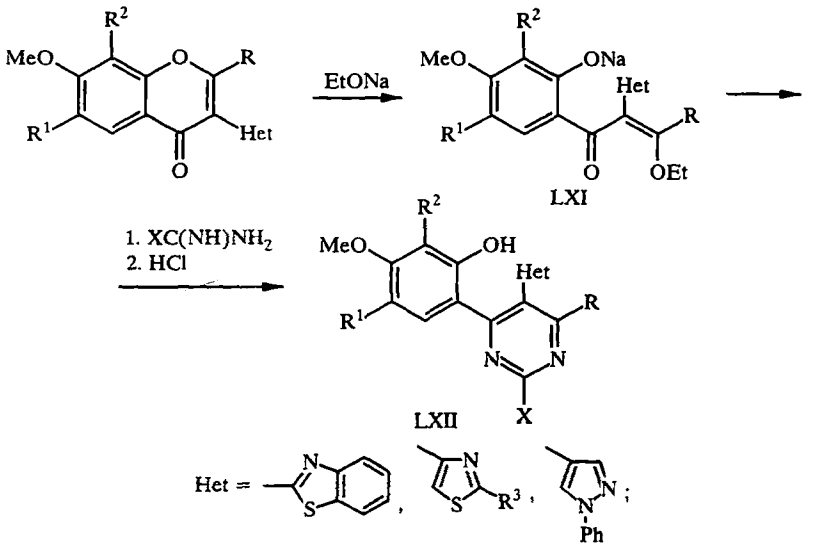
R = H, Me, CF_3, CO_2Et

However, heating of 3-hetarylchromones lacking a substituent at $C_{(2)}$, but possessing an isoxazole [48], 2-thiazole [110], 2-benzothiazole or 2-benzimidazole residue [40, 41], with hydroxylamine in anhydrous pyridine leads exclusively to 2-amino-3-hetarylchromones LX, whose formation may be attributed to consecutive recyclization and isomerization [51]:



2.4. Reaction with amidines

The reaction of 3-hetarylchromones with amidines in the presence of sodium ethylate gives pyrimidine derivatives LXII as the result of opening of the pyrone ring and subsequent addition of amidine to the resultant enol LXI [40, 41, 111, 112]. This reaction may be used for the synthesis of substituted pyrimidines, whose preparation by other methods would be very difficult or even impossible.

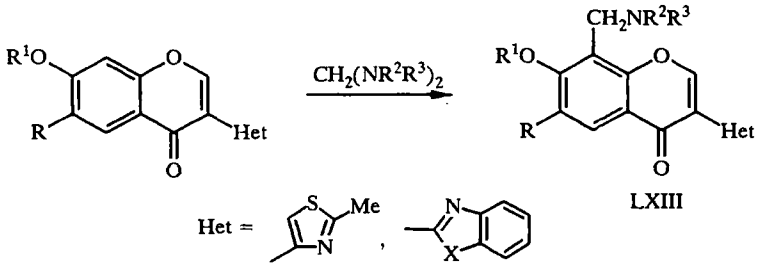


R = H, CF_3; X = H, Me, NH_2; R^1 = H, Et, Pr; R^2 = H, OMe; R^3 = H, Me, Ph

2.5. Reaction with electrophilic reagents

The chromone system contains two sites of enhanced electron density - at $C_{(6)}$ and $C_{(8)}$. Thus, the action of bis(dimethylamino)methane on thiazole [16, 48], benzothiazole [40, 41], and benzimidazole analogs of isoflavone [43] in absolute dioxane leads to 8-dimethylaminomethyl derivatives LXIII. We have recently shown that bis(diethylamino)methane, 1,1′-methylenebispiperidine, or 4,4′-methylenebismorpholine may be used for aminomethylation of 3-benzothiazolyl- and 3-benzimidazolylchromones [113].

The replacement of hydrogen atom in the 1-NH group by CH_2NMe_2 was also observed in the case of pyrazolylchromones [47] upon reaction with bis(dimethylamino)methane. If $C_{(8)}$ is substituted, alkylation proceeds at $C_{(6)}$ [48].

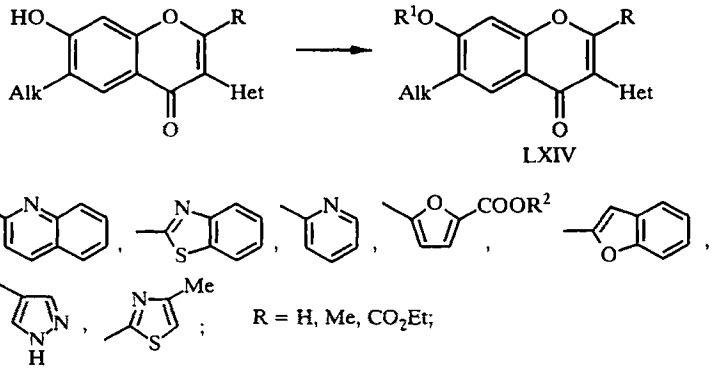


R = H,Alk; R^1 = H, Me; X = S, NMe, NH;
$R^2 = R^3$ = Me, Et; $R^2R^3 = (CH_2)_5$, $CH_2CH_2OCH_2CH_2$

The reactions with bromine [16, 48, 109] and iodine [109] proceed analogously. When excess bromine is used and the reaction time is prolonged, bromination occurs at both $C_{(6)}$ and $C_{(8)}$ of the chromone system.

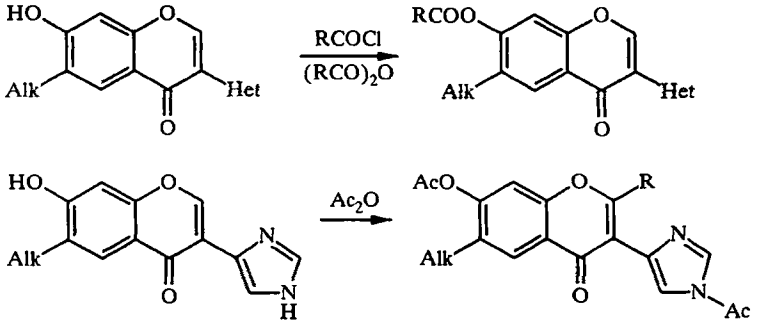
2.6. Alkylation and acylation reactions

In previous work [18, 20, 32, 40-47, 57, 59, 61, 114], we have shown that 3-hetarylchromones containing 7-OH group are alkylated by alkyl halides and dimethyl sulfate in acetone or dioxane in the presence of potassium carbonate to give the corresponding 7-alkoxy derivatives LXIV. The ethoxycarbonyl group at $C_{(2)}$ of the chromone system facilitates these reactions.



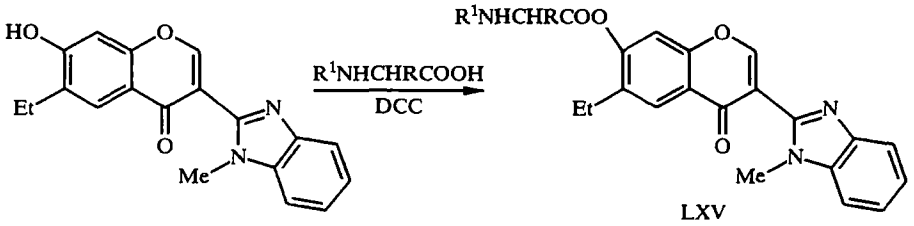
R^1 = Me, Et, CH_2Ph, $CH_2C_6H_4NO_2$-*p*, CH_2COOEt, CH_2CN; R^2 = Me, Et

Quaternary salts are formed from alkyl halides and 3-azahetarylchromones when potassium carbonate is not used [18, 20, 57, 64]. Acylating reagents acylate hydroxyl groups [38, 40, 48, 50, 59, 63] and also the NH groups in the heterocyclic residue [47, 63]:



R = Me, Ph, C_6H_4OMe-*p*, 2-furoyl

The reaction of benzimidazole analogs of isoflavones with N-substituted amino acids in the presence of dicyclohexylcarbodiimide (DCC) in tetrahydrofuran and dimethylformamide gives the corresponding N-protected amino acid esters LXV [42].

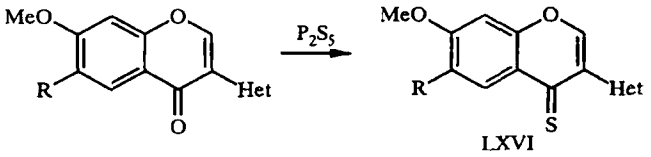


LXV

R = Me, Pr-*i*, $(CH_2)_4NHBoc$; R^1 = Boc, Cbz

2.7. Action of P_2S_5

Heating of 3-hetaryl-7-methoxychromones with P_2S_5 in pyridine gives their thioxo analogs LXVI, which are highly colored in contrast to the colorless starting chromones [17, 20, 52, 53, 106].

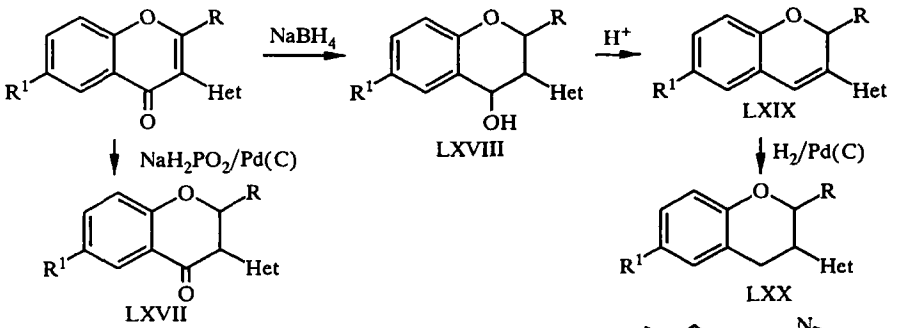


LXVI

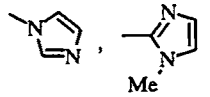
2.8. Reduction of the pyrone ring

Cozzi et al. [70-72] have studied the reactions of 3-imidazolylchromones and found that the action of sodium hypophosphite on these derivatives over palladium black gives 2,3-dihydro-3-imidazolylchromones LXVII [72].

In the case of a stronger reducing agent, namely, sodium borohydride in methanol, 3-imidazolylchromones [70, 72] and their 2,3-dihydro derivatives [71] are reduced to chromanols LXVIII, which are dehydrated under the action of HBr to give chromenes XLIX. In turn, chromenes XLIX are hydrogenated by hydrogen over palladium black in acetic acid to give chromans LXX. In the case of a 2-ethoxycarbonyl or 6-methoxy substituent, these groups undergo saponification to the carboxyl or hydroxyl group, respectively. These reactions may be used to synthesize partially hydrogenated isoflavones, which cannot be obtained by other methods.

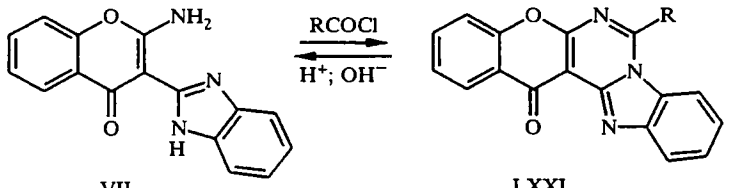


R = H, Me, COOEt, COOH; R^1 = H, Cl, Br, OMe, OH; Het =



2.9. Transformations involving the heterocyclic residue

The reactions of 3-hetarylchromones involving the heterocyclic residue have not been studied extensively. Thus, new polynuclear heterocyclic systems LXXI were obtained by the action of carboxylic acid anhydrides and chlorides on 2-amino-3-(2-benzimidazolyl)chromones VII [68]. Under conditions of both acid and base catalysis, LXXI are converted to the starting compounds.



VII LXXI

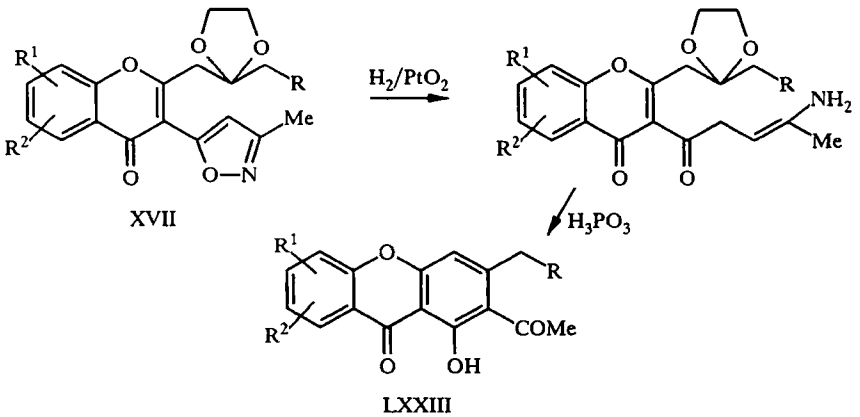
R = Me, Pr, Ph

The condensation of 3-(2-amino-4-thiazolyl)chromones XXI with various α-bromoacetophenones in ethanol gives 3-(6-arylimidazo[1,2-*b*]thiazol-3-yl]chromones LXXII [19].

XXI LXXII

R= H, Cl, Me; R^1 = H, Me; Ar = Ph, C_6H_4Cl-*p*, C_6H_4Br-*p*, $C_6H_4NO_2$-*p*

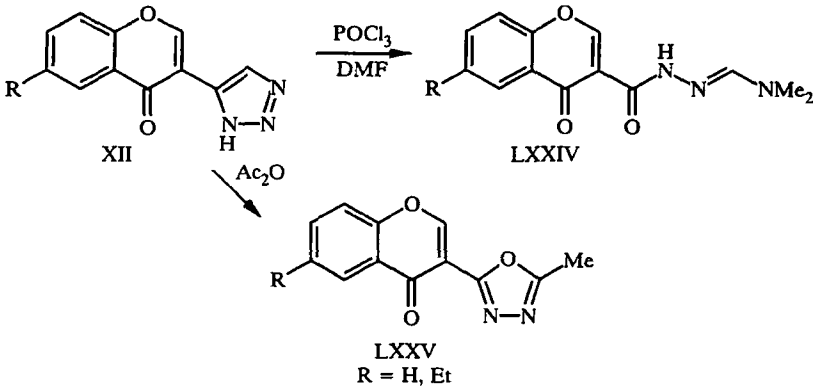
Isoxazole analogs of isoflavones XVII were used as starting compounds for the synthesis of xanthone derivatives LXXIII [80].



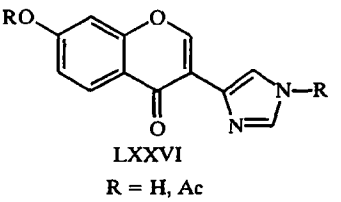
XVII LXXIII

R = H, COOAlk; R^1, R^2 = Alk, OAlk

The reaction of tetrazolyl analogs of isoflavones XII with the Vilsmeier reagent proceeds with opening of the tetrazolyl ring and formation of carbohydrazones LXXIV [2], while reaction with acetic anhydride gives 3-oxadiazolylchromones LXXV [3].



The capacity of 3-imidazolylchromones LXXVI to form complexes with copper salts has been studied [115]. Complexes CuX_2L_2 were obtained, where L = LXXVI, X = Cl, Br, and NO_2. The reaction of equimolar amounts of $CuBr_2$ and chromone LXXVI (R = H) also gives a complex, $CuBr_2L$.



Thus, the data on the synthesis and properties of 3-hetarylchromones indicate that these compounds may be important synthones for obtaining substituted nitrogen heterocycles such as pyrimidines, pyrazoles, and isoxazoles.

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