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NUCLEOPHILIC VINYL SUBSTITUTION IN THE SYNTHESIS OF HETEROCYCLES*. (REVIEW)

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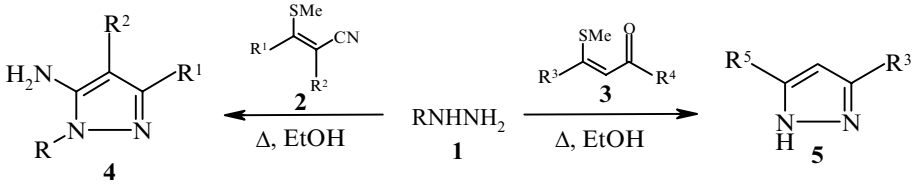
Published data on the synthesis of various heterocyclic compounds by the reaction of nucleophiles with electrophilic olefins containing a nucleophilic group are reviewed and analyzed.

Keywords: reactions of hydrazine, hydroxylamine, guanidine, aromatic and heterocyclic amines, azine and azolium salts, aliphatic, aromatic and heterocyclic CH acids; nucleophilic vinyl substitution.

The data published during the last ten years on the synthesis of heterocyclic compounds by nucleophilic vinyl substitution are reviewed in the present paper. The interest in such reactions is due to the fact that until now they have been among the main methods for the synthesis of substituted heterocycles exhibiting various types of biological activity and also their intermediates. Widely known reviews have been devoted to this matter [1-7], in particular to the mechanism of vinyl substitution [4, 5], the features of the reactions in relation to the structure of the vinyl substrate [6], and the stereochemistry of the process [7]. The data have been arranged with respect to the types of compounds containing a nucleophilic center.

1. REACTIONS OF HYDRAZINE AND ITS DERIVATIVES

The reaction of hydrazines **1** with methylthioethylenes **2**, **3** in boiling ethanol takes place by a mechanism of substitution of the readily leaving methylthio group with the formation of the substituted pyrazoles **4**, **5** with yields of 72-79% [8-10]. Potential leishmanicides were found among them [11]:



R = H, Me; R^1 = NH_2, NHAr, 4-Me(Ph, Ar, Het)- 1,4-diazin-1-yl; R^2 = CN, $CONH_2$, COOEt, Ar; R^3 = PhNH, NHAr, 4-methyl-1,4-diazin-1-yl; R^4 = Ph, Ar, EtO; R^5 = Ph, Ar, OH

* Dedicated to the 100th anniversary of the birth of Prof. Yakov Lazarevich Gol'dfarb.

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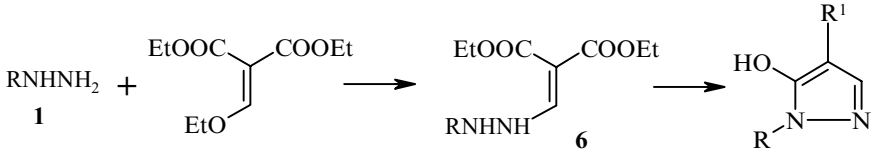
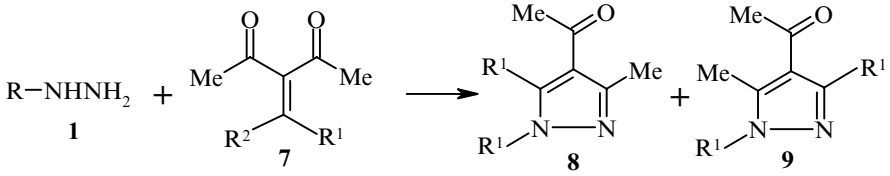
On the basis of the above reaction a method was proposed for the synthesis of 5-hydroxy-1-methylpyrazole with a yield of 76% (1 h at 0°C, followed by boiling for 1 h in alcohol) [12]. The product is an intermediate for the production of herbicides. In the case of hydrazine **1** (R = Ar, Het) after boiling in ethanol the acyclic substitution products **6** were isolated with yields of 57-92% [13]:



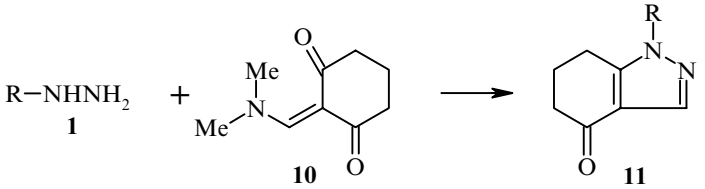
R = Me, Ar, Het; R^1 = H, COOEt

It was reported that a mixture of the respective pyrazoles **8** and **9** was formed in the reaction of the R-methylene derivative of acetylacetone **7** with substituted hydrazines **1** [14, 15]. Here it has been noticed that in the case of alkyl-substituted hydrazine **1** the nitrogen atom attached to radical acts as the nucleophilic center, as witnessed by predominance of compound **8** in the reaction mixture. If arylhydrazines are used, structures **9** are formed preferentially, indicating that the nucleophilic center is displaced toward the amino group.



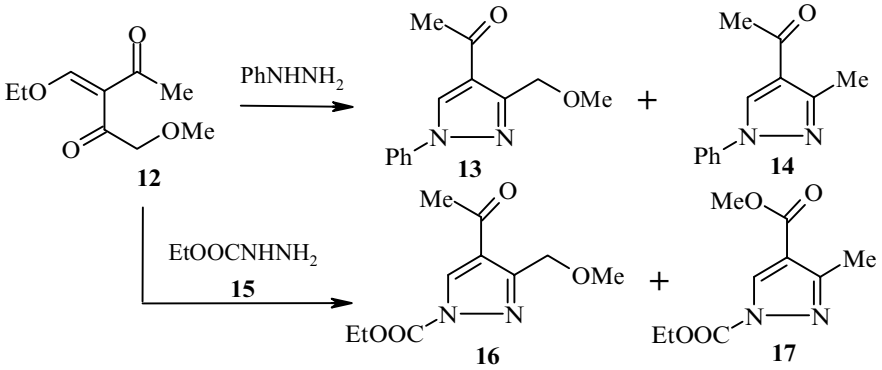
R = H, Me, Ph, $PhCH_2$; R^1 = H, NH_2; R^2 = Et, Me_2N, MeS

At the same time, only indazoles **11** are formed in the case of the reaction of hydrazines **1** with enamine **10**:

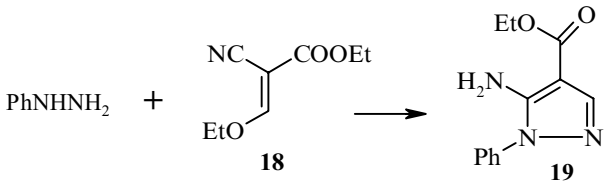


R = Me, Ph

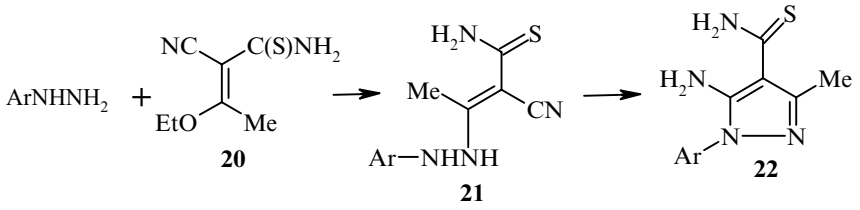
The reaction of ethoxyethylene **12** with phenylhydrazine leads to the formation of a mixture of the corresponding pyrazoles **13** and **14** in equal ratios, while the hydrazine derivative **15** under the same conditions gives a mixture of the products **16** and **17** correspondingly in a ratio of 7:1:



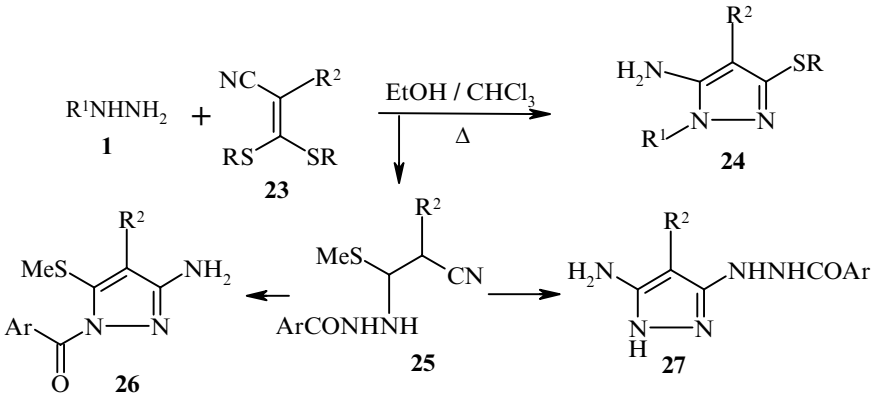
The reaction of phenylhydrazine with ethoxymethylenecyanoacetic ester **18** gave the corresponding 5-aminopyrazole **19** [16]:



In the reaction of arylhydrazines with the ethoxymethylene derivative of cyanothioacetamide **20** in chloroform the linear substitution product **21** is formed. When heated to 80-85°C in potassium hydroxide solution (or when boiled for 8 h in acidic medium) it undergoes cyclization to pyrazole **22** [17]:

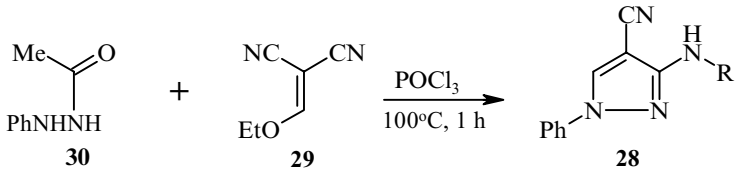


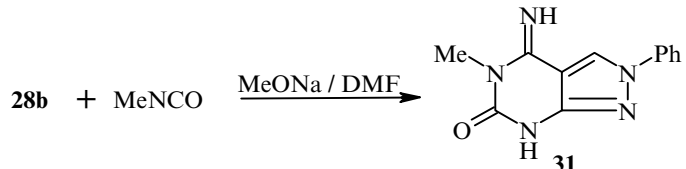
The reaction of hydrazines **1** with unsaturated nitriles **23** gives 5-amino-4-(N-furfurylcarbamoyl)-pyrazoles **24** with yields of 60-79%. In the case of hydrazine **1** (where R^1 = ArCO) the substitution products **25**, which undergo cyclization to compounds **26**, were obtained with yields of 50-95%. The same product **25** gives compound **27** with 54% yield when heated in alcohol with $N_2H_4 \cdot H_2O$ for 6 h at 50°C [18, 19]:



R = Me, Et, $PhCH_2$; R^1 = H, Ph, Bz, ArCO; R^2 = N-furfurylcarbamoyl, COOEt

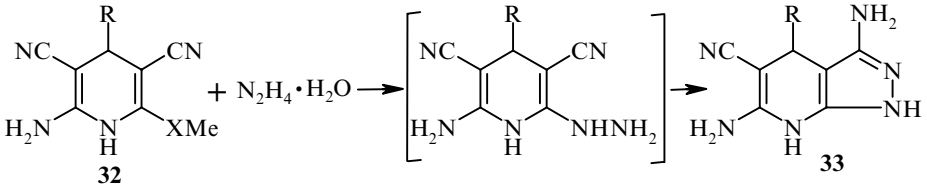
Compound **28a**, obtained with a yield of 32% by the reaction of ethoxymethylenemalononitrile **29** and disubstituted hydrazine **30**, was converted into pyrazole **28b** when boiled in acidic medium. When treated with MeNCO in the presence of MeONa in nitrogen atmosphere at 60°C for 12 h compound **28b** is transformed into the cycloaddition product 4-imino-5-methyl-2-phenyl-4,5-dihydropyrazolo[3,4-*d*]pyrimidin-6(7H)-one (**31**) [20]:





28 **a** R = $CH=C(CN)_2$, **b** R = H

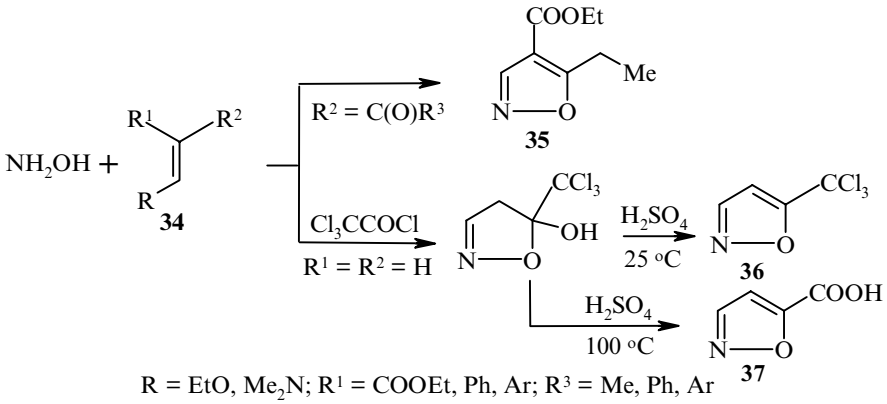
The nucleophilic substitution of 2-methoxy (thio, seleno) groups in the series of 1,4-dihydropyridines was studied. Thus, boiling of methylchalcogenopyridines **32** in alcohol in the presence of excess of hydrazine hydrate gave high yields of the partly hydrogenated pyrazolopyridines **33** [21]:



R = 2-Cl–C_6H_4; X = O, S, Se

2. REACTIONS OF HYDROXYLAMINE

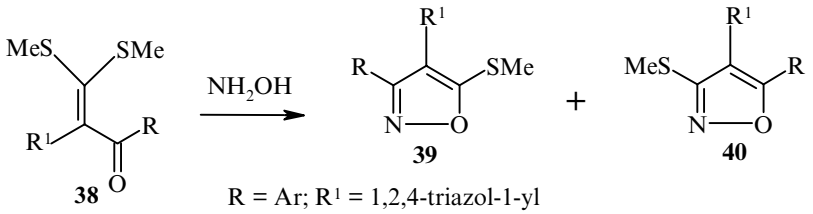
The reaction of hydroxylamine with ethoxy and dimethylaminoethylenes **34** in aqueous alcohol for 24 h gave 80-91% yields (or 90-99% in the MeOH/MeONa/Na_2CO_3 system, at boiling for 2 h) of the corresponding isoxazoles **35**-**37** [22-24]:



R = EtO, Me_2N; R^1 = COOEt, Ph, Ar; R^3 = Me, Ph, Ar

The cyclocondensation of methylthioethylenes **38** with hydroxylamine in alcohol in the presence of barium hydroxide or sodium ethoxide gave 5-methylthioisoxazole **39** (yield 42-49%) and 3-methylthioisoxazole **40** (yield 15-21%). The formation of two products indicates that the nucleophilic center may be both the amino group and the hydroxy group of hydroxylamine. The relatively high yields of isoxazole **39** indicate preferential participation of the latter in the substitution of the nucleofugic group.

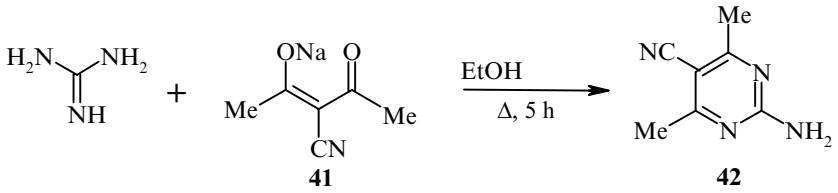
In preliminary bioinvestigations 5-methylthioisoxazoles **39** were found to exhibit growth-regulating activity [25]:



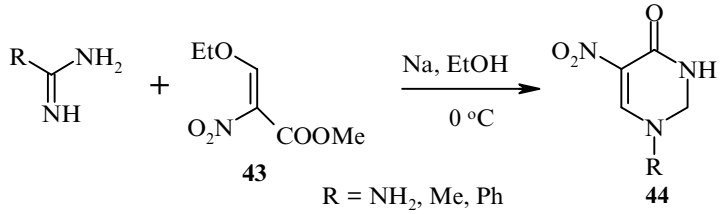
R = Ar; R[1] = 1,2,4-triazol-1-yl

3. REACTIONS OF UREA, THIOUREA, GUANIDINE, AND THEIR ANALOGS

2-Aminopyrimidine **42** is produced if guanidine is boiled with unsaturated nitrile **41** in ethanol for 5 h [26]:

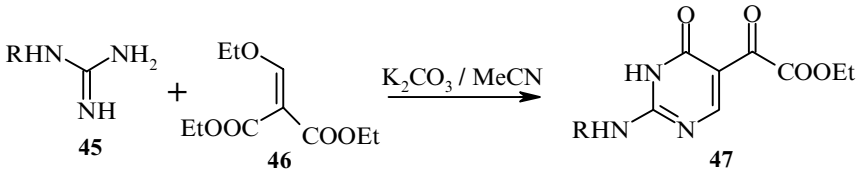


The reaction of guanidine and its analogs with methyl 3-ethoxy-2-nitroacrylate (**43**) in absolute alcohol in the presence of sodium methoxide at 0°C gave 4-pyrimidinones **44** [27]:



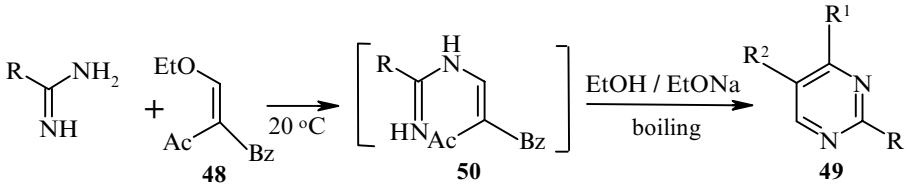
R = NH_2, Me, Ph

When boiled with ethoxymethylenemalonate **46** in acetonitrile in the presence of potassium carbonate 2-guanidinobenzimidazole **45** forms 4(3H)-pyrimidinone **47**, which exhibits anti-HIV activity *in vitro* [28]:



R = benzimidazol-2-yl

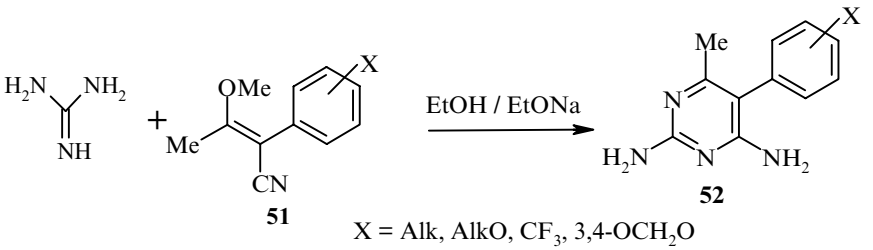
Pyrimidines **49** were obtained with yields of 20-40% by the reaction of S-methylisothiourea or benzamidine with functionally substituted ethoxyethylenes **48** in absolute ethanol in the presence of sodium ethoxide (1-2 h at 20°C, followed by boiling for 1 h) [29, 30]:



R = MeS, Ph; R^1 = Me, Ph; R^2 = Bz, Ac

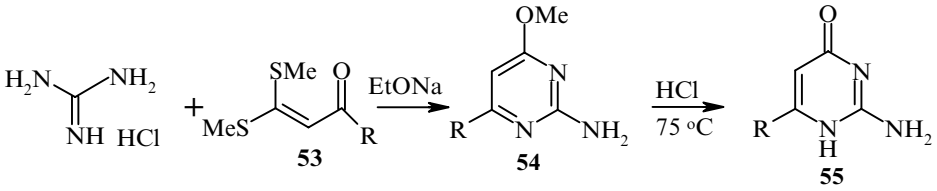
It is significant that in this case the cyclization of the adduct **50** takes place both with participation of the Ac group (when R^1 = Me, R^2 = Bz) and with participation of the Bz group (R^1 = Ph, R^2 = Ac).

The cyclization of guanidine with methoxyethylene **51** in an alcohol solution of sodium ethoxide leads to pyrimidines **52**, which are potential antimalarial preparations [31]:



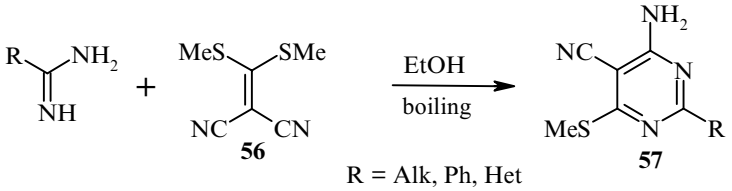
X = Alk, AlkO, CF_3, 3,4-OCH_2O

The reaction of guanidine hydrochloride with di(methylthio)ethylene **53** in absolute benzene or methanol in the presence of sodium ethoxide in atmosphere of nitrogen at 60°C gives pyrimidine **54**, which transforms into pyrimidinone **55** when kept in acidic medium (75°C, 20 h) [32]:



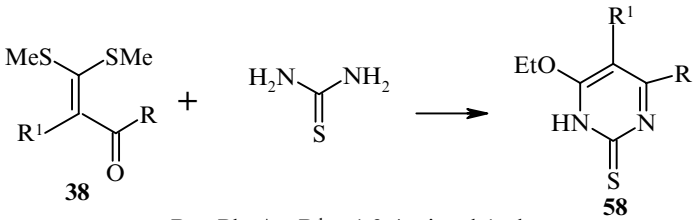
R = 5-amino-7-methoxynaphth-2-yl

4-Aminopyrimidines **57**, suitable for use as leishmanicides, were obtained when the substituted ethylene **56** was boiled for 3 h with amidines in alcohol in the presence of triethylamine [33]:



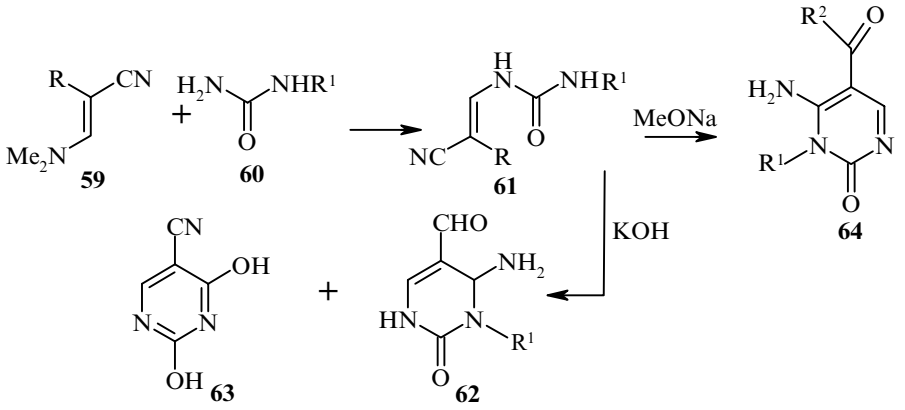
R = Alk, Ph, Het

The condensation of methylthioethylenes **38** with thiourea in alcohol gave pyrimidines **58** [25]:



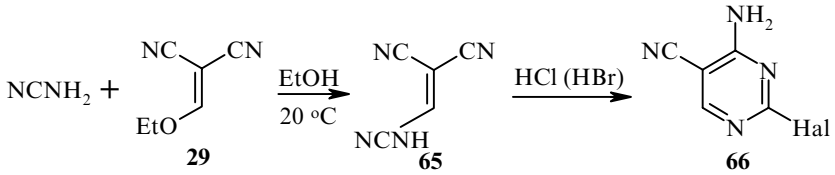
R = Ph, Ar; R^1 = 1,2,4-triazol-1-yl

The reaction of nitriles **59** with substituted ureas **60** gave the product from nucleophilic substitution **61** with yield of 50-55%. Cyclization of the product under alkaline conditions led to 4-amino-2(1H)-pyrimidinones **62** and 5-cyano-2,4-dihydropyrimidine **63**. When the reaction was carried out in the presence of sodium methoxide in methanol or sodium ethoxide in ethanol, only 6-amino-2(1H)-pyrimidinones **64** were obtained with yields of 50-79% [34]:



R = CHO, COOEt; R^1 = H, Me, Et, Ph; R^2 = Me, Et

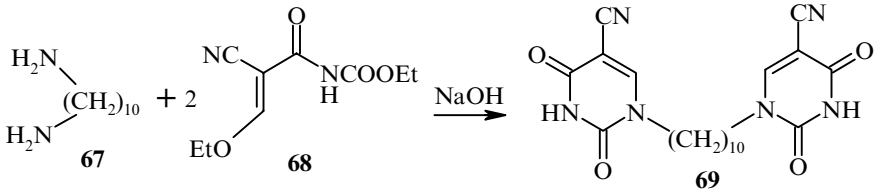
The reaction of cyanamide with ethoxymethylenemalononitrile **29** in alcohol at room temperature for 15 min leads to the nucleophilic substitution product **65** with yield of 95%. In the presence of hydrochloric or hydrobromic acid the product undergoes cyclization to 4-amino-5-cyano-2-halopyrimidine (**66**) [35]:



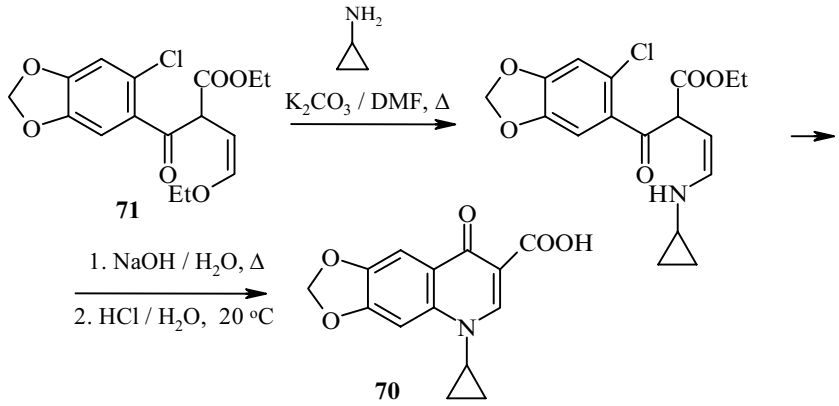
Hal = Cl, Br

4. REACTIONS OF ALIPHATIC AND ALICYCLIC AMINES

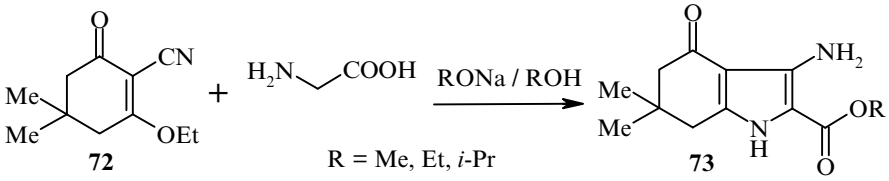
When 1,10-diaminodecane (**67**) was heated with 3-ethoxy-2-ethoxycarbonylcarbamoylacrylonitrile (**68**) in a ratio of 1:2 in alkaline medium, the pyrimidine derivative **69** was obtained [36]:



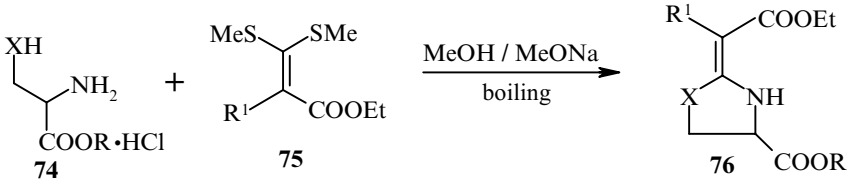
The antibacterial activity of 5-cyclopropyl-8-oxo-5,8-dihydro-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylic acid (**70**), obtained by the reaction of cyclopropylamine with ethoxymethylene derivative **71**, has been mentioned. The first stage of the process takes place at cooling with ice followed by stirring at 20°C for 1 h; the second stage is initiated by heating and finishes with hydrolysis [37]:



Tetrahydroindoles **73** were synthesized by the reaction of 3-ethoxycyclohex-2-en-1-one **72** with glycine [38]:

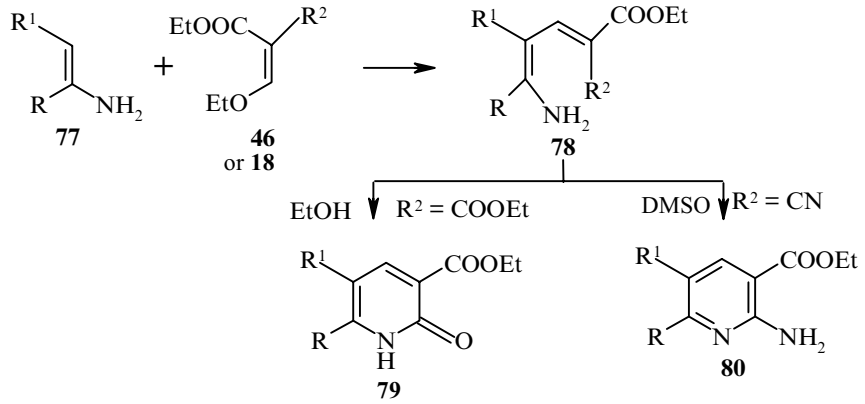


2-Ylideneoxazolidines and 2-ylidenethiazolidines **76** are formed when the esters of β-mercapto- or β-hydroxy-substituted amino acids **74** are boiled with dimethylthioethylenes **75** in methanol or ethanol in the presence of sodium methoxide for 1-10 h [39]:



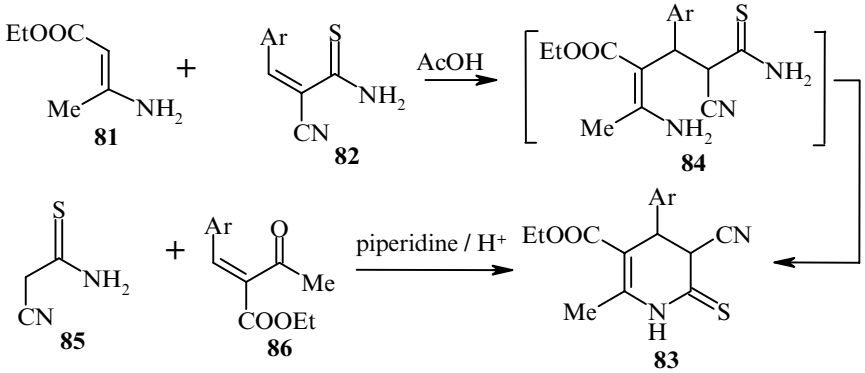
R = Me, Et; R^1 = Me, Et, Ac, Bz, COOEt, CN; X = O, S

In reaction with ethoxymethylenemalonate **46** in an aprotic solvent (benzene, chloroform) or with ethoxymethylenecyanoacetic ester **18** (alcohol) at 20°C for 24-48 h the unsaturated amines **77** form the corresponding vinyl substitution products **78**, which undergo cyclization to 2-pyridinones **79** when heated in alcohol, the yields being 86-97% [40]. After boiling in DMSO or 1:2 mixture of DMSO and toluene 2-aminopyridines **80** were obtained with yields of 72-83% [41]:



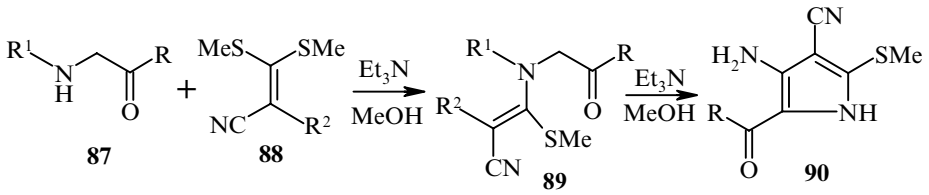
R = EtO, NH_2, BuNH, Ar, NHAr; R^1 = COOEt, CN

The condensation of unsaturated amine **81** with arylidenecyanothioacetamide **82** in acetic acid gives 2-pyridinethiones **83** with yield of 54%. The reaction probably takes place through a stage involving the formation of the Michael adducts **84**, which undergo cyclization by nucleophilic substitution mechanism. Evidence for this is provided by the independent synthesis of 2-pyridinethiones **83** from cyanothioacetamide **85** and the arylidene derivative **86** [42]:



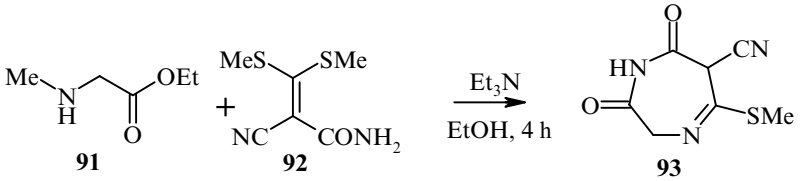
Ar = Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$Me_2NC_6H_4$

The condensation of secondary amines **87** with di(methylthio)ethylenes **88** in boiling ethanol or methanol in the presence of triethylamine gives unsaturated nitriles **89**. The cyclization of the latter in the presence of triethylamine (boiling in methanol or ethanol) leads to pyrroles **90** with yields of 18-39% [43]:

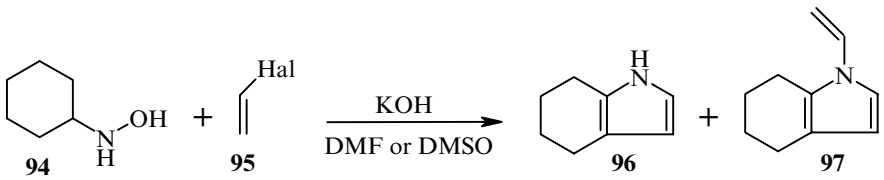


R = EtO, MeO, NH_2; R^1 = H, Me; R^2 = CN, COOEt, $CONH_2$

In the reaction of amine **91** and di(methylthio)methylenecyanoacetamide **92** under analogous conditions tetrahydrodiazepine **93** was obtained with yield of 73%:

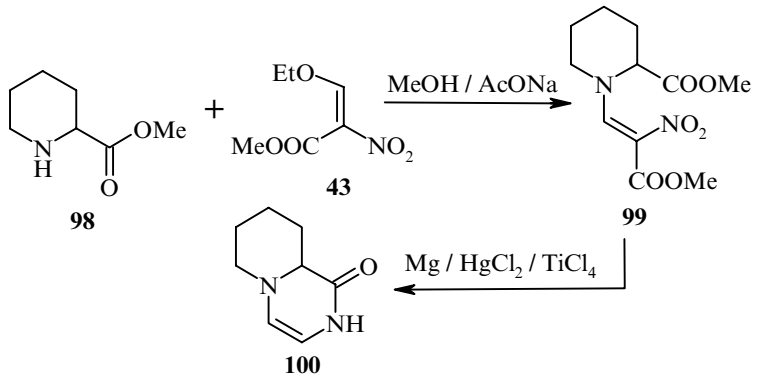


The reaction of N-cyclohexylhydroxylamine (**94**) with vinyl halides **95** in DMF or DMSO in the presence of potassium hydroxide led to the formation of a mixture of condensed pyrroles **96** and **97** with yields of 43% and 22% respectively [44]:

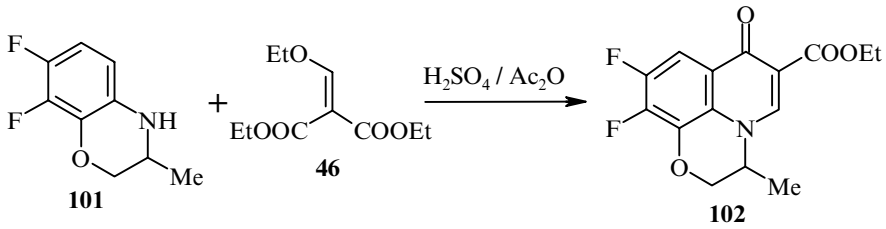


Hal = Cl, Br

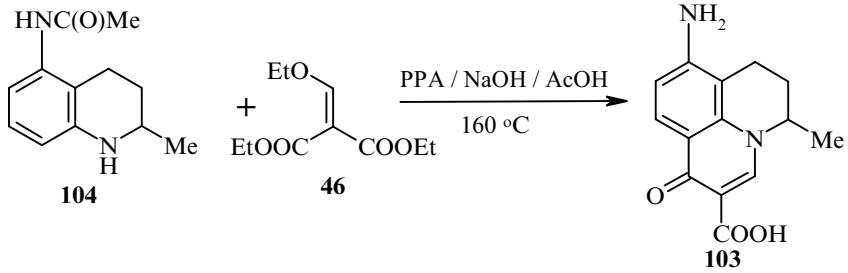
The reaction of 2-methoxycarbonylpiperidine (**98**) with ethoxyethylene **43** in methanol/sodium acetate gave the condensation product **99**, which was converted into compound **100** by treatment with $Mg/HgCl_2/TiCl_4$ in THF–BuOH [45]:



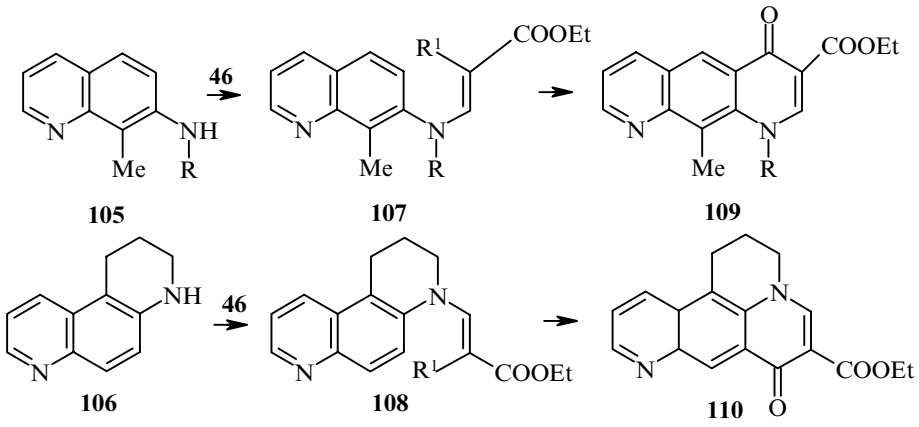
The reaction of dihydrobenzoxazine **101** with ethoxymethylenemalonic ester **46** gave compound **102**, which is a potential antibacterial agent [46]:



A method has been proposed for the synthesis of 8-amino-5-methyl-1-oxo-6,7-dihydro-1H,5H-benzo[*i*,*j*]quinolizine-2-carboxylic acid (**103**), which has antibacterial activity. One of the concluding stages of the synthesis is the reaction of 5-acetamido-2-methyl-1,2,3,4-tetrahydroquinoline (**104**) with ethoxymethylenemalonic ester **46** in alcohol at 160°C in the presence of polyphosphoric acid and then in methanol with sodium hydroxide followed by treatment with sodium hydroxide in methanol and acidification with acetic acid [47]:



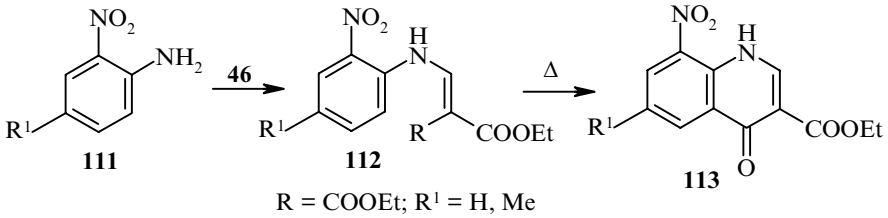
The reaction of quinolines **105** and pyridoquinolines **106** with ethoxymethylenemalonate **46** without a solvent at 170°C gives the nucleophilic substitution products **107** and **108**, which undergo cyclization when heated at 260°C in a stream of nitrogen for 1 h with the formation of compounds **109** and **110** (yields 79-90%) [48]:



R = H, Et; R^1 = COOEt

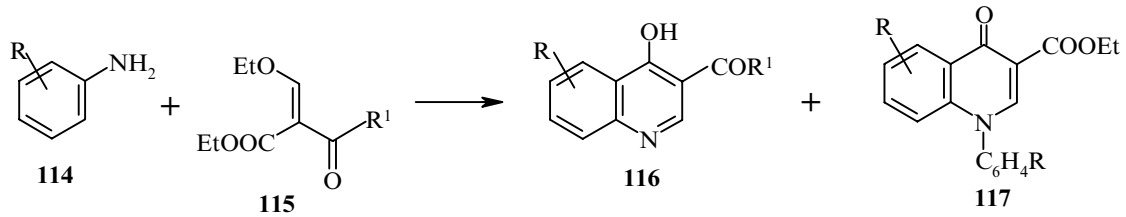
5. REACTIONS OF AROMATIC AMINES

Most of the papers on the reactions of substituted anilines with ethoxymethylenemalonic ester describe the formation of nucleophilic substitution products, which undergo cyclization to the corresponding 4-quinolinones during thermal treatment. Biologically active compounds were found among the latter [49, 52-57]. Thus, during the reaction of 2-nitroanilines **111** with ethoxymethylenemalonic ester **46** the substitution products **112** were isolated. They underwent cyclization to quinolones **113** when heated at 240°C in Dowtherm for 5 h (yields 64-76%). The obtained quinolones exhibit antiallergic activity [49]:



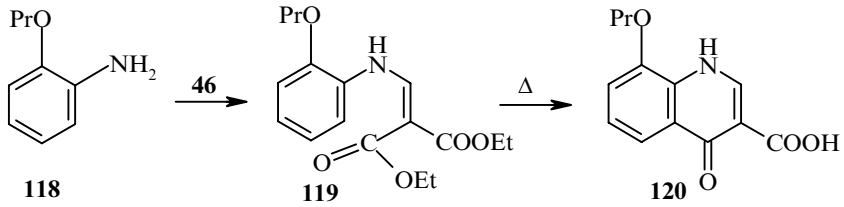
R = COOEt; R^1 = H, Me

The reaction of substituted anilines **114** with ethyl 3-ethoxy-2-R-acrylates **115** under heating in DMF in the presence of potassium carbonate or in 1,4-dioxane in the presence of potassium *tert*-butoxide gave substituted quinolines **116** with yields of up to 86% [50, 51]. Substances with bactericidal characteristics were found among 1-R-4,5-halo-4-quinolinones **117** [52]. Compounds **117** were obtained from ethoxyethylenes **115**, where R^1 = 2,4,5-trihalophenyl, and cyclization is realized with the participation of the nucleofugic group, the halogen, and the amino group of aniline **114**:

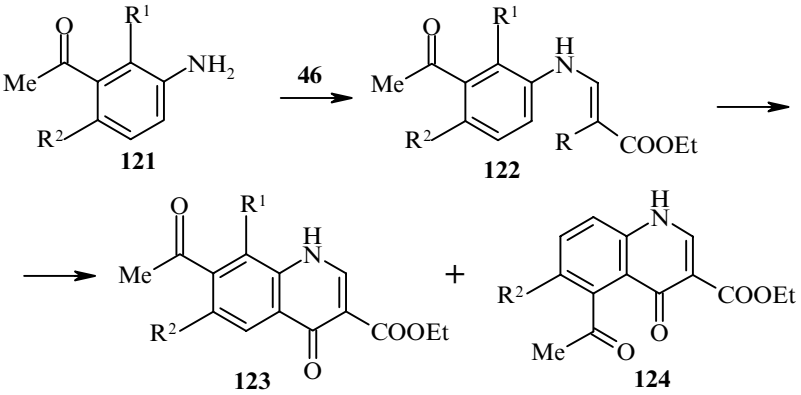


R = H, Alk, AlkO, 3-Cl-4-X-5-F-C_6H_3; R^1 = Alk, EtO, 2-Cl-4-X-5-C_6H_2;
R^2 = H, R-phenyl; X = Cl, F

When 2-propoxyaniline (**118**) was heated with ester **46** at 140°C for 1 h the compound **119** was obtained which on heating at 250°C for 1 h in diphenyl ether and subsequent hydrolysis was converted into 4-oxo-8-propoxy-1,4-dihydroquinoline-3-carboxylic acid (**120**). The latter was patented as an agent for the treatment of allergic complaints caused by antigen–antibody reaction, such as asthma, dermatitis, conjunctivitis, etc. [53]:

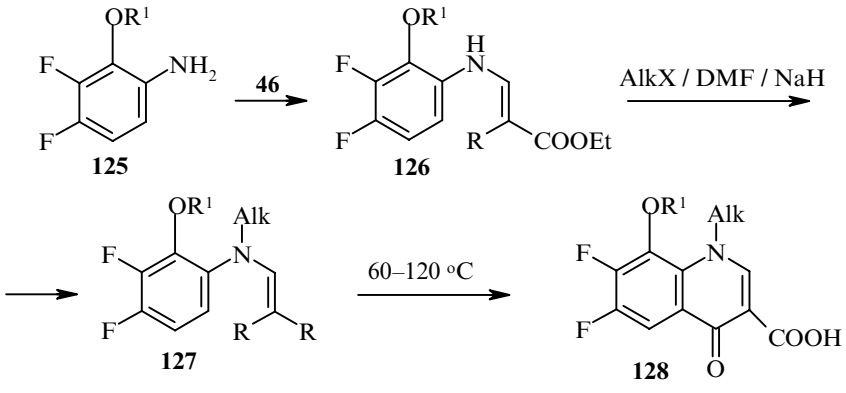


The reaction of substituted 3-acetylaniline **121** with ethoxymethylenemalonic ester **46** in toluene gave the substitution product **122**, which during cyclization (R^1 = H) formed a mixture of 7-substituted quinolines **123** and **124**. The latter are potential antibacterial agents [54]:



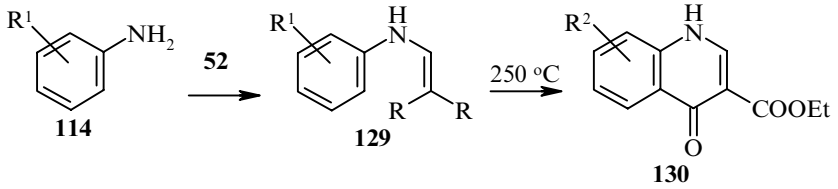
R = COOEt; R^1 = R^2 = H, F; R^1 = H, R^2 = F

The reaction of 2-alkoxy-3,4-difluoroanilines **125** with ethoxymethylenemalonate **46** gave compounds **126**. The latter were converted by alkylation into esters **127**, the thermal cyclization of which in polyphosphoric acid esters followed by hydrolysis led to a quantitative yield of the derivatives of 4-quinolonecarboxylic acids **128**, possessing bactericidal activity [55]:



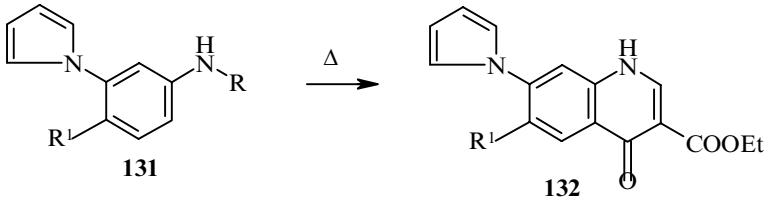
R = COOEt; R^1 = Me, Et

The substitution products **129** were obtained by heating of 3- or 4-furylanilines **114** with ethoxymethylenemalonate **46** up to 100-110°C for 2 h. The products were converted into 6- and 7-(2-furyl)-1,4-dihydro-4-oxopyridine-3-carboxylic acids **130** by heating at 250°C in Dowtherm. The antibacterial activity of their 1-ethyl derivatives was noted [56]:



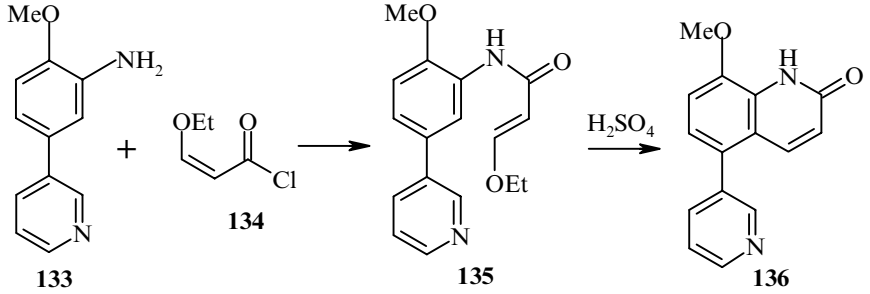
R = COOEt; R^1 = 3- or 4-(2-furyl); R^2 = 6- or 7-(2-furyl)

Ethoxymethylenemalonate **46** reacts similarly with pyrrole **131a**, and the formation of the intermediate product **131b** indicates a mechanism of nucleophilic substitution at the first stage of the synthesis of quinolone **132** [57]. The latter possess antibacterial and fungicidal activity.

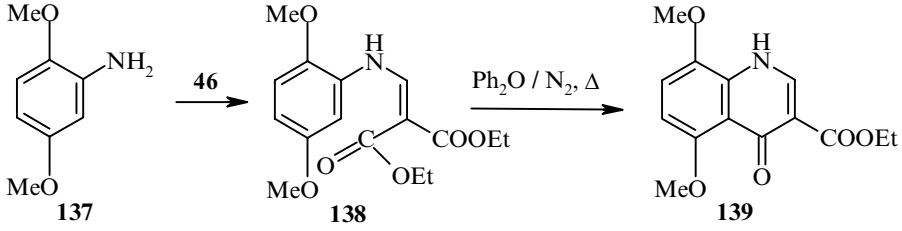


a R = H, **b** R = $(EtOOC)_2C=CH$; R^1 = Cl, Me

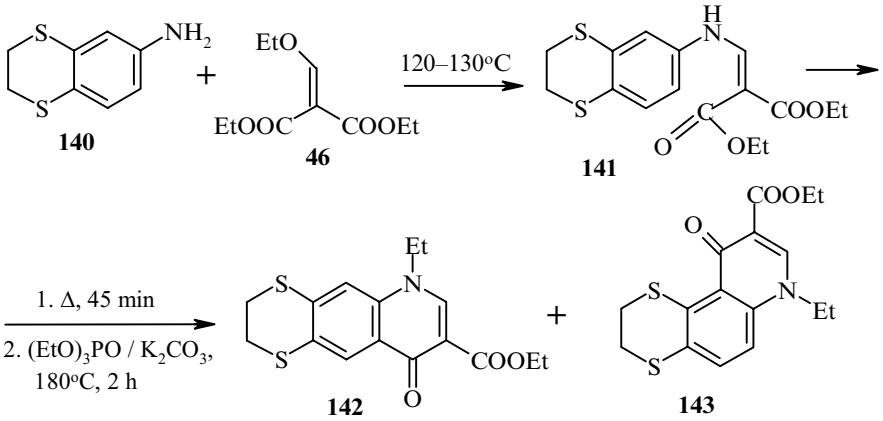
Quinolin-2(1)-one **136** is obtained by the reaction of 2-methoxy-5-(3-pyridyl)aniline (**133**) with acid chloride **134**; the reaction includes the cyclization of the intermediate **135** in an acidic medium by a nucleophilic substitution mechanism [58]:



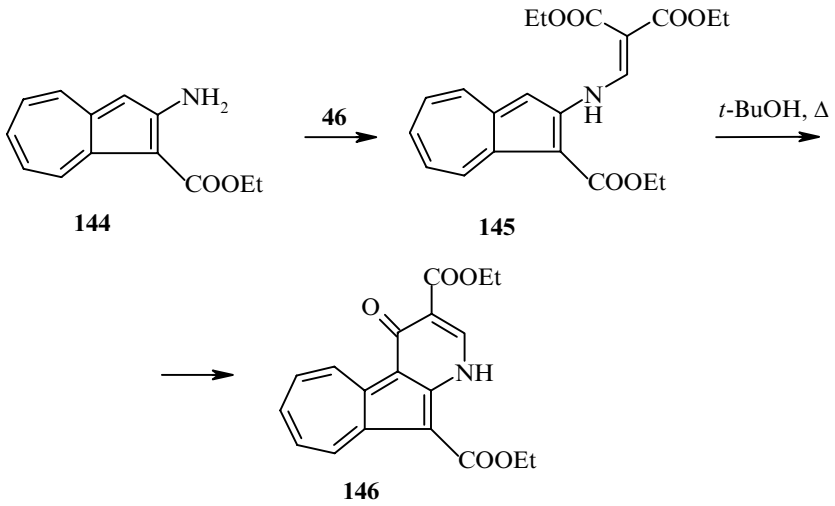
The substitution product **138** was obtained with yield of 59% by boiling dimethoxyaniline **137** with ethoxymethylenemalonic ester **46** in benzene for 4 h. When boiled in diphenyl ether in nitrogen atmosphere for 15 min the compound **138** underwent cyclization to quinoline **139** with yield of 71% [59]:



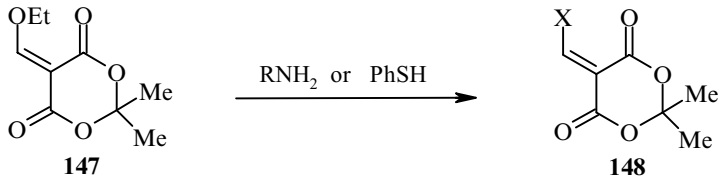
The synthesis of ethylenedithio derivatives of quinoline was realized by heating a mixture of aniline **140** and ethoxymethylenemalonate **46** at 120-130°C. The stable intermediate **141** was formed with yield of 70-75%. When heated at 253-258°C followed by alkylation by the action of $(EtO)_3PO$ (potassium carbonate, 180°C, 2 h) it underwent cyclization to compounds **142** and **143** with yields of 55% and 45% respectively [60]:



The reaction of the five-membered annellated aromatic amine **144** with ethoxymethylenemalonic ester **46** in alcohol for 64 h led to the nucleophilic substitution product **145** with yield of 95%. When the product was boiled in *tert*-butyl alcohol for 5 days, a high yield of compound **146** was obtained [61]:

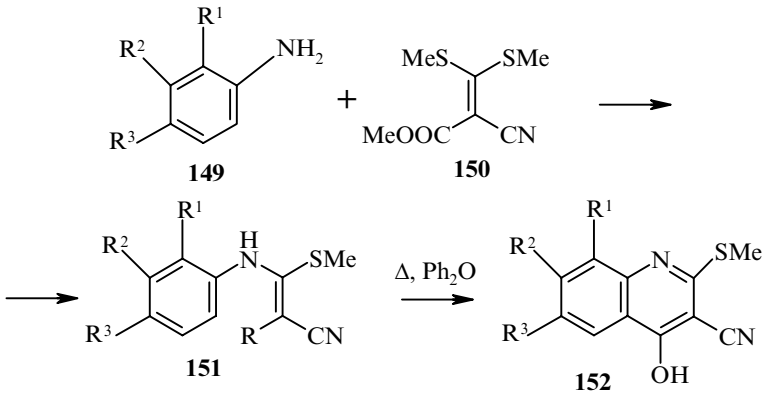


Microwave treatment during the nucleophilic substitution reactions of ethoxymethylene derivative of Meldrum's acid **147** with anilines or thiophenol led to the corresponding compounds **148** with yields of 80-97% [62]:



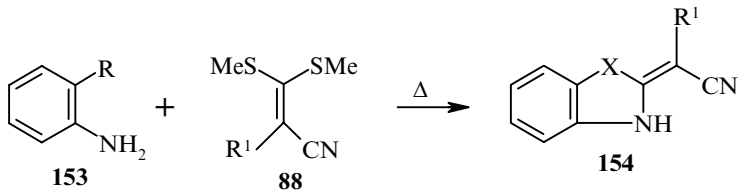
X = PhNH, ArNH, PhS

As in the case of ethoxyethylenes, during the reaction of substituted anilines **149** with di(methylthio)methylenecyanoacetic ester **150** the substitution products **151** are formed at the first stage. When boiled in diphenyl ether at 235°C for 0.5 h they undergo cyclization to the corresponding quinolines **152** [63]:



R = COOMe; $R^1 = R^2 = R^3 = H$; R^1 = MeO, Cl;
R^2 = MeO; R^3 = Me, MeO, Cl, Br

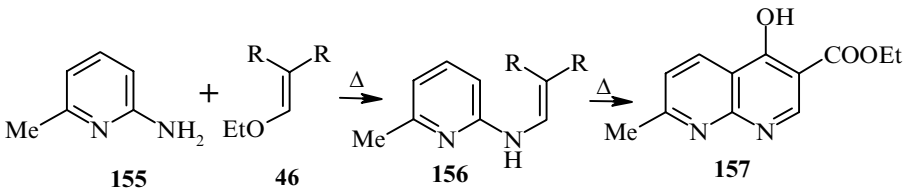
When *ortho*-substituted anilines **153** are boiled with methylthioethylenes **88** the partially hydrogenated condensed compounds **154** are formed with yields of 90-95% [64]:



R = SH, OH, NH_2; R^1 = CN, COOEt; X = S, O, NH

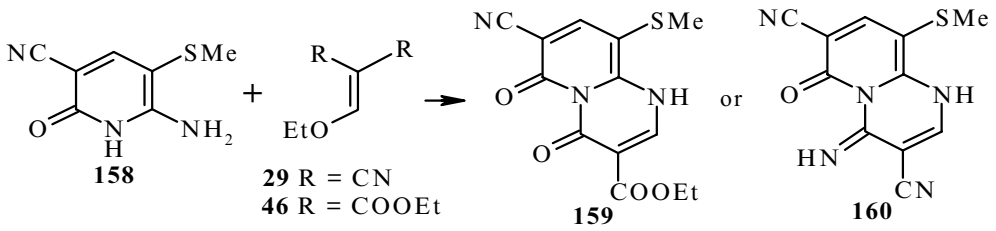
6. REACTIONS OF HETEROAROMATIC AMINO DERIVATIVES

The reaction of 2-amino-6-methylpyridine (**155**) with ethoxymethylenemalonic ester **46** gives the linear substitution product **156**. After further boiling in diphenyl ether the product undergoes cyclization to 1,8-naphthyridine **157**, which is of interest as a potential antimalarial agent [65]:

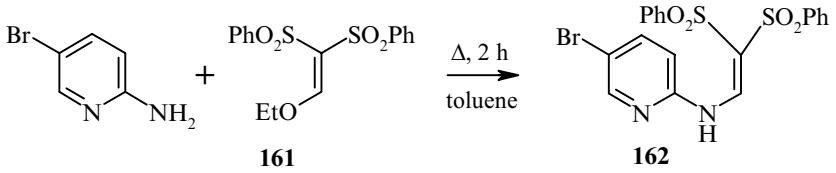


R = COOEt

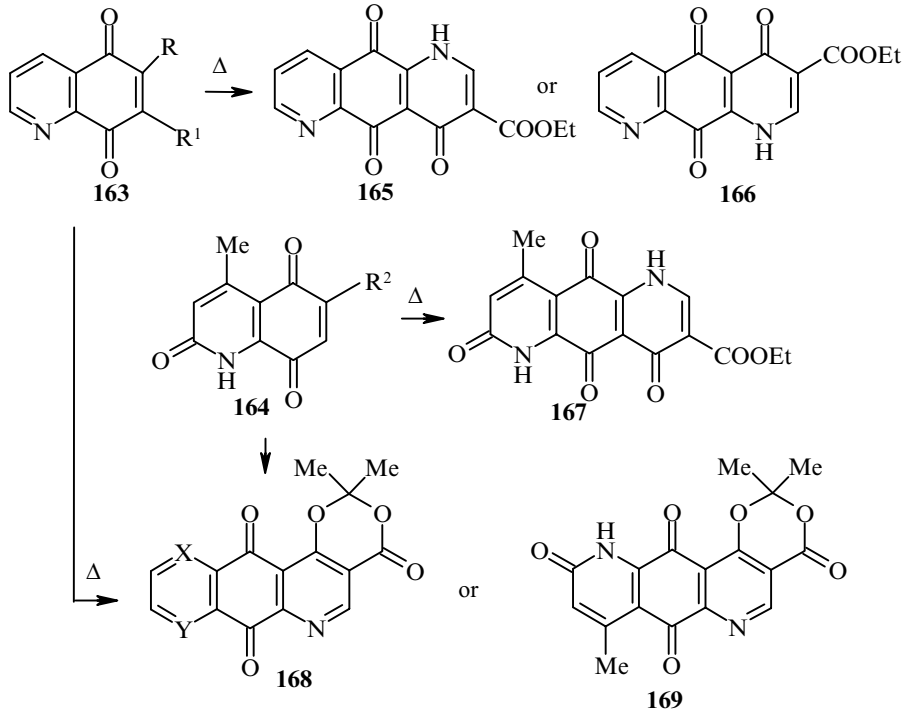
In the case of the polysubstituted 2-aminopyridine **158** cyclization at position 3 of the pyridine ring is impossible. Its reaction with ethoxymethylenemalonic ester **46** or ethoxymethylenemalononitrile **29** leads to the formation of pyrido[1,2-*b*]pyridines **159** or **160** respectively [66]:



Cases where the intermediate products of cyclocondensation possess biological activity have been described in the literature. Thus, when 2-amino-5-bromopyridine was boiled in toluene with ethoxyethylene **161** the substitution product **162**, patented as an agent for the treatment of arthritis, was obtained [67]:

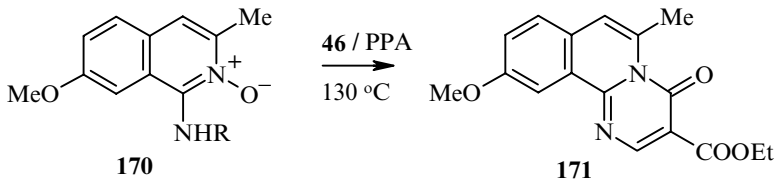


During the condensation of 6-R-7-R-quinoline-5,8-quinones **163a**,**b** or of 6-R-4-methyl-(1H)-2,5,8-quinolinetrione **164a** with ethoxymethylenemalonate **46** in the presence of trifluoroacetic acid the corresponding products from nucleophilic substitution **163c**,**d**, **164b** are formed. Their thermal cyclization leads to diazaanthracenes **165-167**. The condensation of compounds **163a**,**b** and **164a** with Meldrum's acid in the presence of $HC(OMe)_3$ followed by thermal cyclization gives the heterocycles **168**, **169** [68]:



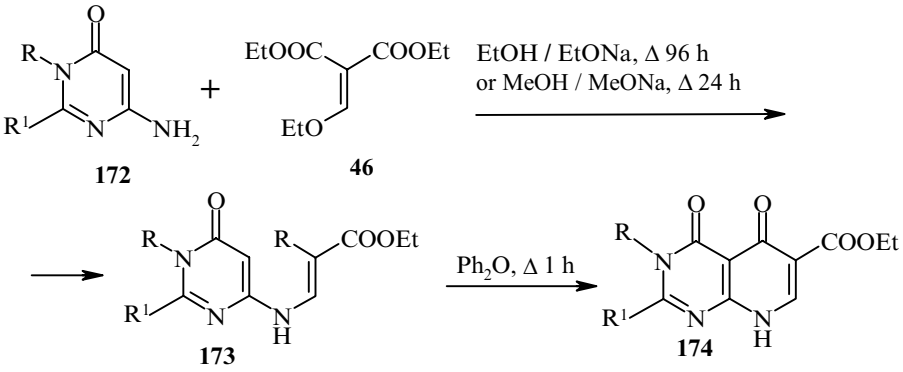
163 a R = NH_2, R^1= H; **b** R^1= NH_2, R = H; **c** R = $(EtOOC)_2C$=CHNH, R^1 = H;
d R^1= $(EtOOC)_2C$=CHNH; **164 a** R^2 = NH_2, **b** R = $(EtOOC)_2C$=CHNH; X = N, CH; Y = CH, N

When isoquinoline N-oxide **170a** was boiled with ethoxymethylenemalonic ester **46** compound **170b** was formed. Treatment of the product with polyphosphoric acid at 130°C led to the potentially bioactive pyrimido[2,1-*a*]isoquinolin-4-one **171** [69]:



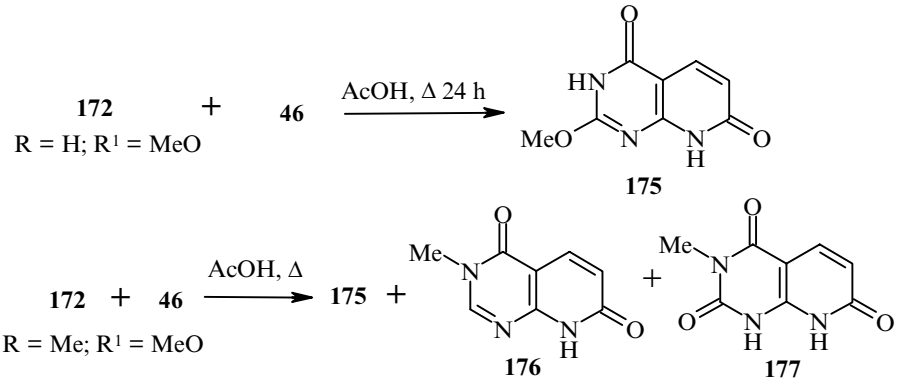
a R = H, **b** R = $(EtOOC)_2C{=}CH$

The reaction of 6-aminopyrimidines **172** with ethoxymethylenemalonate **46** by boiling in various media gave the substitution products **173**, which underwent cyclization to the corresponding condensed systems **174** with yields of 25-38% [70]:

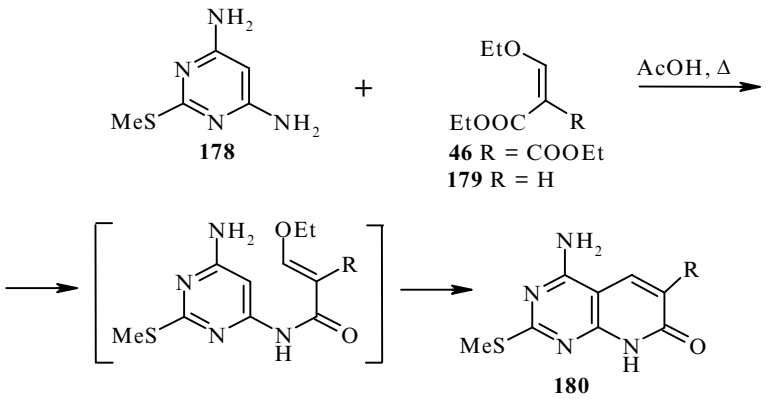


R = H, Me; R^1 = MeO, Et

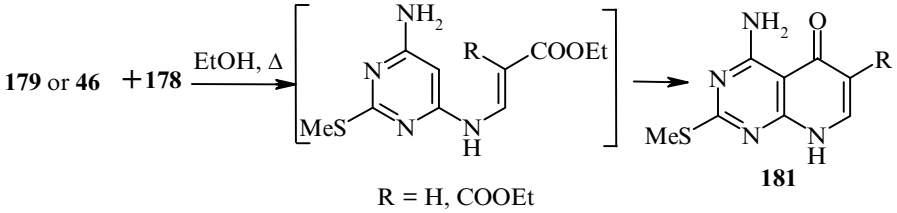
If acetic acid is used as solvent in this reaction a mixture of products **175-177** is formed as a result of cyclocondensation, hydrolysis, and decarboxylation with yields of 68, 13, and 5% respectively:



In the literature there are other data on the cyclocondensation of derivatives of aminopyrimidine with functionally substituted ethoxyethylenes, where the key stage is the formation of N-alkylated product, and substitution takes place at the cyclization stage. Thus, when 4,6-diamino-2-methylthiopyrimidine (**178**) was boiled in acetic acid with ethyl β-ethoxyacrylate **179** or the ethoxymethylenemalonic ester **46** 7-oxopyrido-[2,3-*d*]pyrimidine **180** was obtained with yield of 36% [71]:

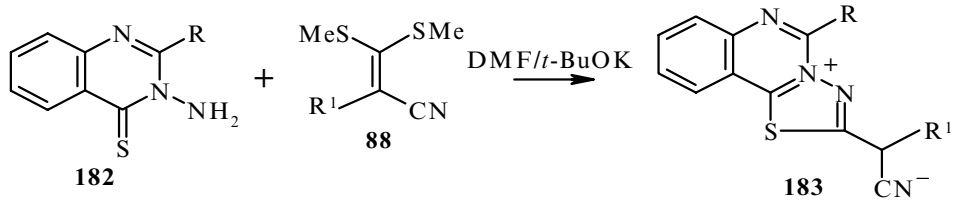


Boiling of the same initial reagents in ethanol leads to the formation of 5-oxopyrido[2,3-*d*]pyrimidine **181** with yield of 85%:



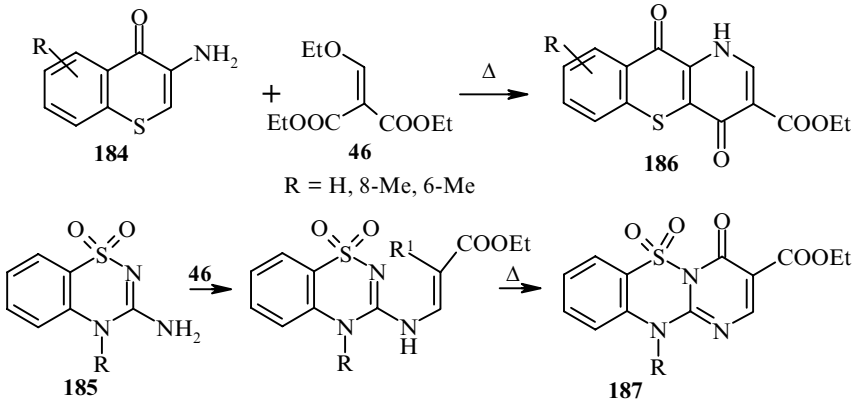
R = H, COOEt

The reaction of 3-aminobenzopyrimidine-4-thione **182** with dimethylthioethylenes **88** in absolute DMF in the presence of potassium *tert*-butoxide gave the bipolar ion **183**, which can be attributed to the class of the polycondensed thiadiazoles [72]:



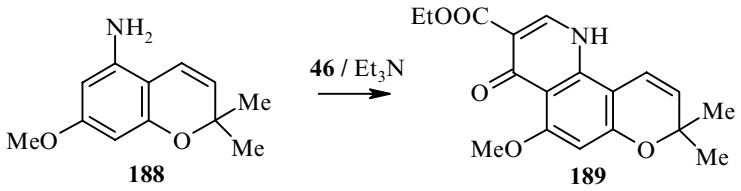
R = *i*-Bu, Ph, Ar; R^1 = COOMe, CN, $CONH_2$

The schemes of the reactions between condensed six-membered sulfur-containing heterocyclic amines **184** (170°C) and **185** (200°C) and esters **46** are given below. In both cases cyclization to the corresponding condensed structures **186**, **187** occurred; the yields being 89 and 75% respectively [73, 74]:

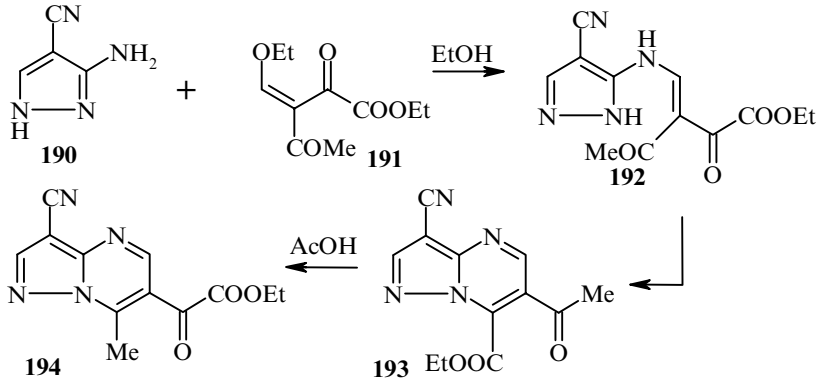


R = Alk, Ph; R^1 = COOEt

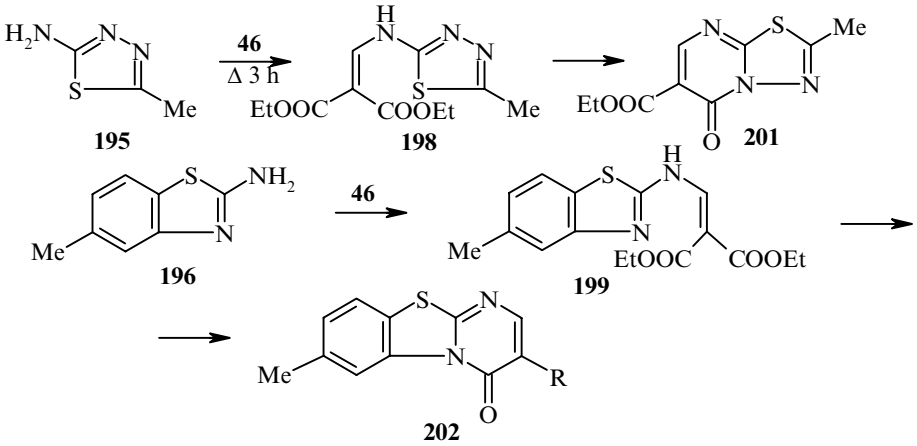
Derivatives of pyrano[2,3-*h*]quinoline were also synthesized. Thus, the condensation of 5-aminochromene **188** with ethoxymethylenemalonic ester **46** in the presence of triethylamine followed by thermal cyclization led to the derivative **189** [75]:

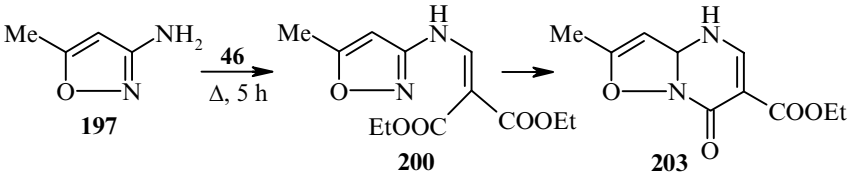


The reaction of 3-amino-4-cyanopyrazole (**190**) with ethoxyethylene **191** has been studied repeatedly. It was established that their reaction in alcohol gave the intermediate **192** with a yield of 98%. This intermediate then underwent regioselective attack by the NH group on the ethoxymethylene fragment with further cyclization to pyrazolo[1,5-*a*]pyrimidine **193**. Treatment of the product with acetic acid (70°C, 5 h) led to recyclization to pyrazolopyrimidine **194** [76]:

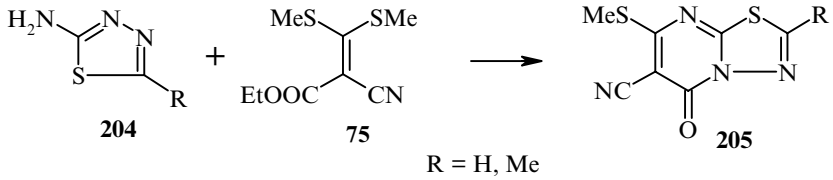


In addition, when the amino derivatives of thiadiazole **195**, benzothiazole **196**, and isoxazole **197** were boiled in alcohol or pyridine with ethoxymethylenemalonic ester **46**, the substitution products **198**-**200** were formed with yields of up to 90%. Further treatment of the latter with polyphosphoric acid (90-100°C) for 3 h led to 6-ethoxycarbonyl-2-methyl-7-oxo-7H-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine (**201**), 3-ethoxycarbonyl-8-methyl-4-oxo-4H-pyrimido[2,1-*b*]benzothiazole (**202**), and 6-ethoxycarbonyl-2-methyl-7-oxo-7H-isoxazolo[2,3-*a*]-pyrimidine (**203**) with yields of 82, 80, and 75% respectively [77]:



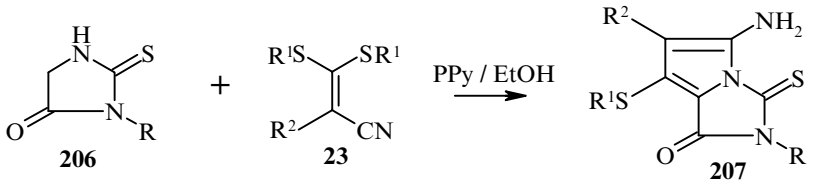


The reaction of the five-membered heterocyclic amines **204** with dimethylthioethylene **75** results in the formation of the cyclocondensation products **205** [78]:



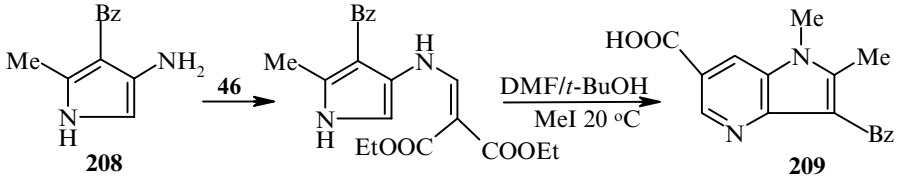
R = H, Me

The reaction of 3-R-2-thioxohydantoins **206** with ethylenes **23** in the presence of piperidine in alcohol gave pyrrolo[1,2-*a*]imidazol-1-ones **207** [79]:

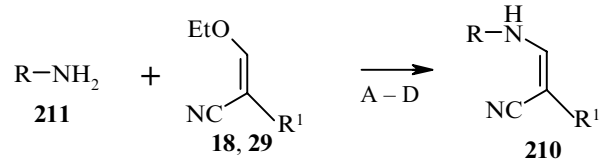


R = H, Ph; R^1 = Me, Et; R^2 = CN, COOEt

3-Benzoyl-7-oxo-4,7-dihydropyrrolo[3,2-*b*]pyridine-6-carboxylic acid (**209**), synthesized by the reaction of 4-amino-3-benzoyl-2-methylpyrrole (**208**) with ethoxymethylenemalonic ester **46**, has antimicrobial activity [80]:

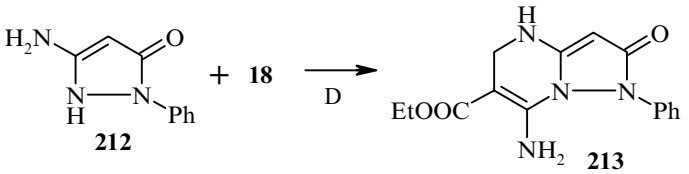


The production and spectral characteristics of derivatives of 3-N-arylamino-2-cyanoacrylic acid **210** have been described [81]. They were produced by the reaction of amines **211** with ethoxyethylenes **18** or **29** by four methods: A) boiling in dry benzene; B) boiling in absolute alcohol for 15-20 h; C) boiling in HMPTA at 100-150°C for 4 h; D) fusion on an oil bath. All four methods led to the products **210**:

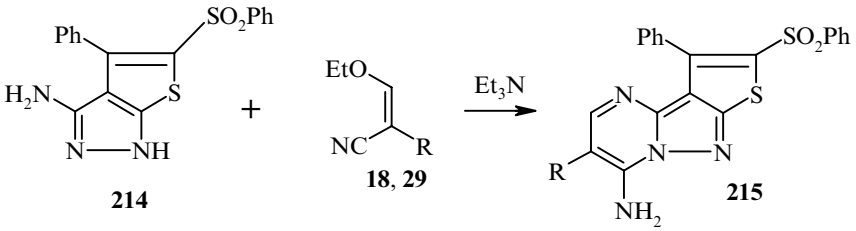


R = 2-phenylbenzoxazol-2-yl, benzothiazol-2-yl, thiazol-2-yl, 4-(benzoxazol-2-yl)phenyl, 3-oxo-2-phenyl-2,3-dihydropyrazol-5-yl, 1-arylbenzimidazol-5-yl; R^1 = CN, COOEt

An exception was the reaction of 5-aminopyrazolone **212** with ethoxymethylenecyanoacetic ester **18** by method D, when the cyclocondensation product **213** was obtained without isolation of the substitution product:

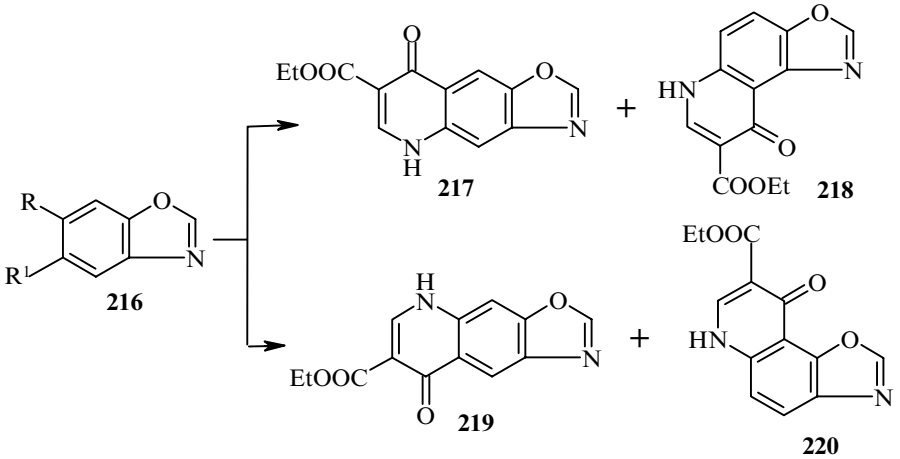


The reaction of thieno[2,3-*c*]pyrazole **214** with ethoxyethylenes **18** or **29** in the presence of triethylamine gave the tricyclic compound **215** [82]:



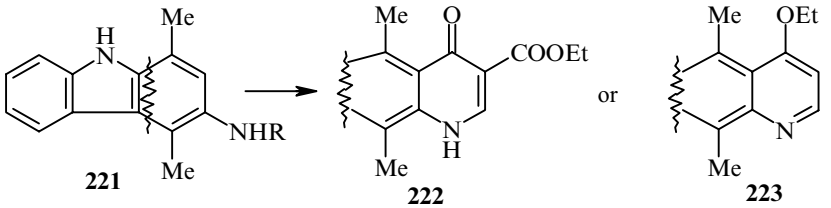
R = CN, COOEt

A mixture of oxazoloquinolines **217** and **218** or **219** and **220** was obtained by the condensation of 2-R-5- or 2-R-6-aminobenzoxazoles **216a**,**b** with ethoxymethylenemalonic ester **46** *via* a stage involving the respective intermediates **216c**,**d** [83]:



a R = NH_2, R^1 = H; **b** R = H, R^1 = NH_2; **c** R = $(EtOOC)_2C{=}CHNH$, R^1 = H;
d R = H, R^1 = $(EtOOC)_2C{=}CHNH$

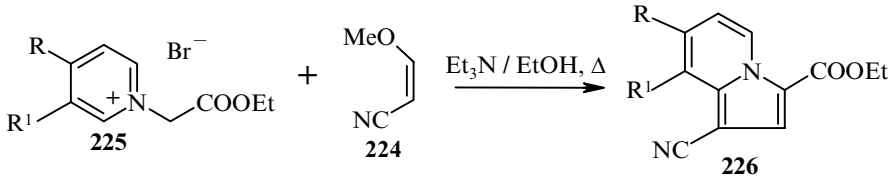
The reaction of 3-amino-1,4-dimethyl-9H-carbazole **221a** with ethoxymethylenemalonic ester **46** in alcohol at 80°C for 1 h gave the substitution product **221b**. The latter underwent cyclization, depending on the conditions, either to condensed 4-pyridone **222** (diphenyl ether, 240°C, 20 min) or to 4-ethoxypyridine **223** (200°C, sublimation) with yields of 44 and 26% respectively [84]. The *in vitro* cytotoxicity of the obtained compounds was discussed:



a R = H, **b** R = $(EtOOC)_2C=CH$

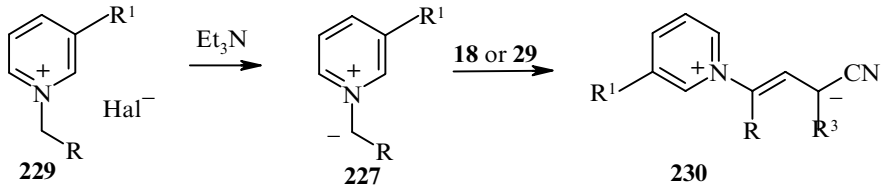
7. REACTIONS OF QUATERNARY AZINIUM AND AZOLIUM SALTS

The reaction of 3-methoxyacrylonitrile (**224**) with 1-(ethoxycarbonylmethyl)pyridinium salts **225** leads to the formation of the products from 1,3-dipolar cycloaddition, i.e., the indolizine derivatives **226**, with yields of 42-63% [85]. However, this reaction can be regarded as nucleophilic substitution taking place by the Ad_N–E mechanism:

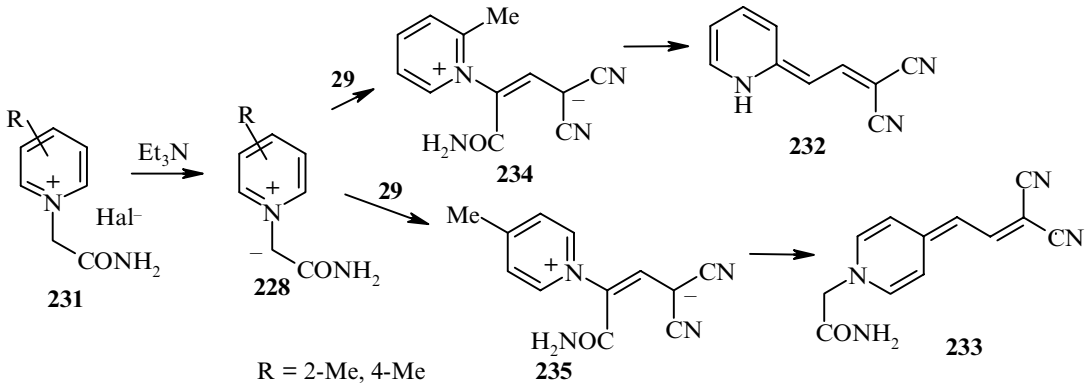


R = R^1 = H, R+R^1 = CH=CH–CH=CH

It was shown that the direction of the reactions of pyridinium ylides **227**, **228**, formed during the action of triethylamine on methylpyridinium salts, with ethoxyethylenes **18** and **29**, depends on the position of the methyl group in the pyridine ring. Thus, 3-methylpyridinium salts **229** form the zwitterions **230** in this reaction. In contrast the reaction of 2- or 4-methylpyridinium chlorides **231** with ethoxymethylenemalononitrile **31** in the presence of an organic base leads to merocyanines **232** and **233**. It was established that the latter are formed through the stage of the corresponding zwitterions **234** and **235** [86]:

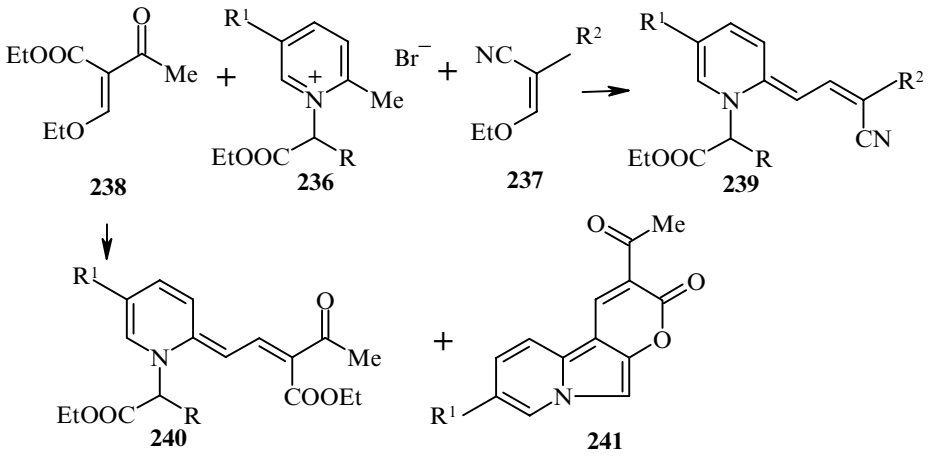


R = $CONH_2$, COAr; R^1 = H, Me; R^3 = COOEt, CN



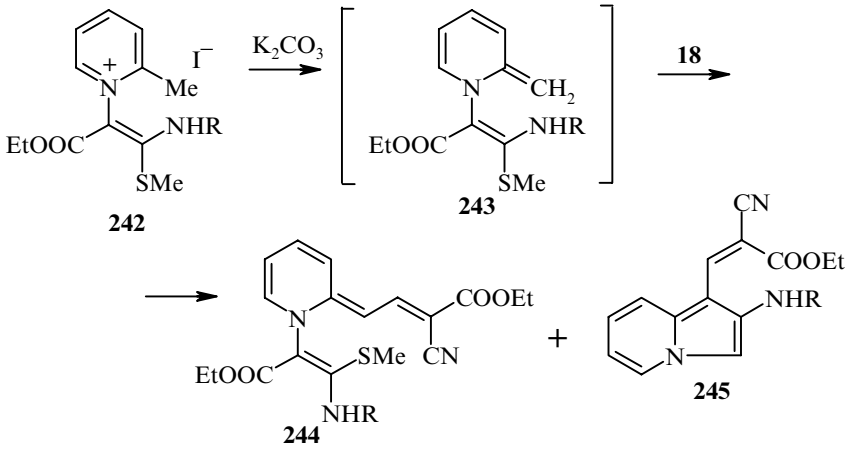
R = 2-Me, 4-Me

The vinyl substitution products **239**, **240** were obtained during the condensation of 1-(α-R-ethoxycarbonylmethyl)-2-methyl-5-R^1-pyridinium bromides **236** with the nitrile **237** and carbonyl **238** derivatives of ethoxyethylene in the presence of potassium carbonate or potassium *tert*-butoxide. In the case of the carbonyl derivatives they were obtained in mixtures with the corresponding cyclic compounds **241** [87]:



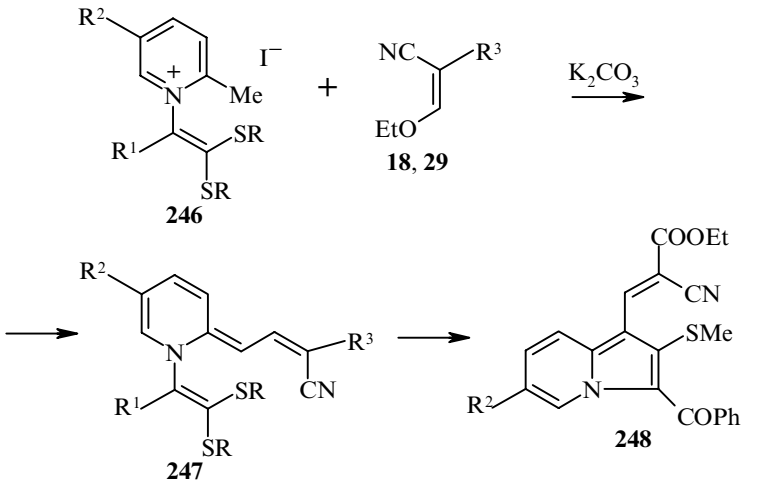
R = R^1 = H, Me, Et; R^2 = CN, COOMe

The anhydro bases **243** were generated by the action of potassium carbonate on 2-methylpyridinium iodides **242**, and they react with ethoxymethylenecyanoacetic ester **18** to form 1,2-dihydropyridines **244** with yields of 93-94%. Traces of indolizines **245** were also found among the reaction products [88]:



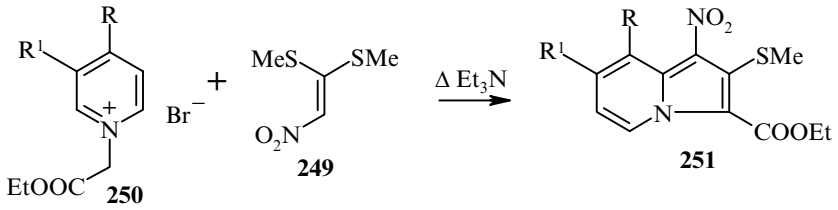
R = Me, C_2H_5

2-Methylpyridinium salts **246** also react similarly with ethoxyethylenes **19**, **31**. Here 2-(3-R-3-cyanoallylidene)-1,2-dihydropyridines **247** were isolated with yields of 40-56%. In the case of compound **246** (R^1 = COPh, R^2 = H, R^3 = COOEt) in order to isolate the pure reaction product it was converted by pyrolysis into indolizine **248** [89]:



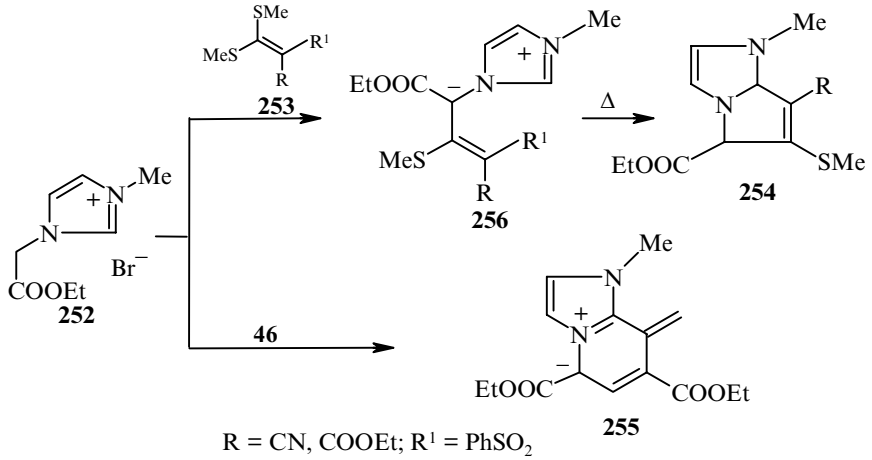
R = Me, Et; R^1 = COOEt, COPh; R^2 = H, Me, Et; R^3 = COOEt, CN

When dimethylthioethylene **249** was boiled with bromides of N-(ethoxycarbonylmethyl)pyridinium derivatives **250** in alcohol in the presence of triethylamine indolizines **251** were formed with yields of 80-93% [90]. The corresponding bromides of isoquinoline react similarly.



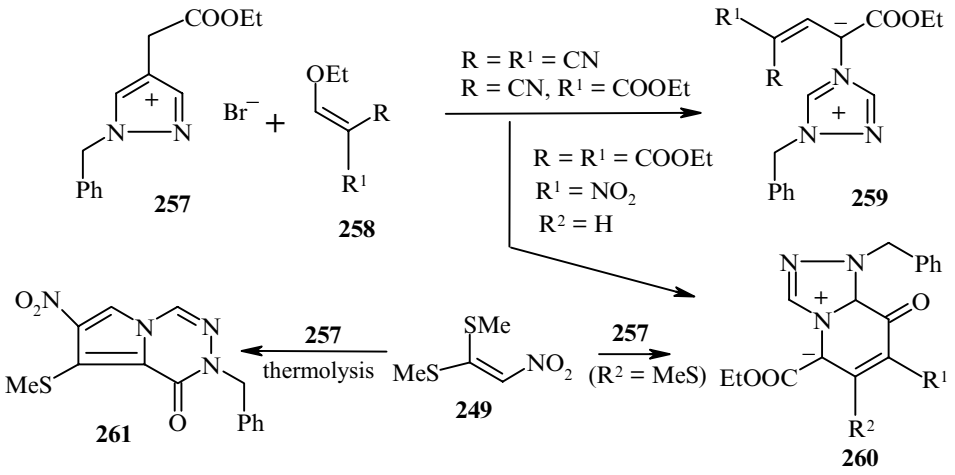
R = R^1 = H; R+R^1 = CH=CH–CH=CH

Imidazolinium bromides **252** form the corresponding condensed systems **254** and **255** with dimethylthioethylenes **253** and ethoxymethylenemalonic ester **46** in chloroform in the presence of potassium carbonate at 25°C for 168 h; the yields being in the order of 60% [91]. The cyclization of the nucleophilic substitution products **256** is initiated by heating in xylene.

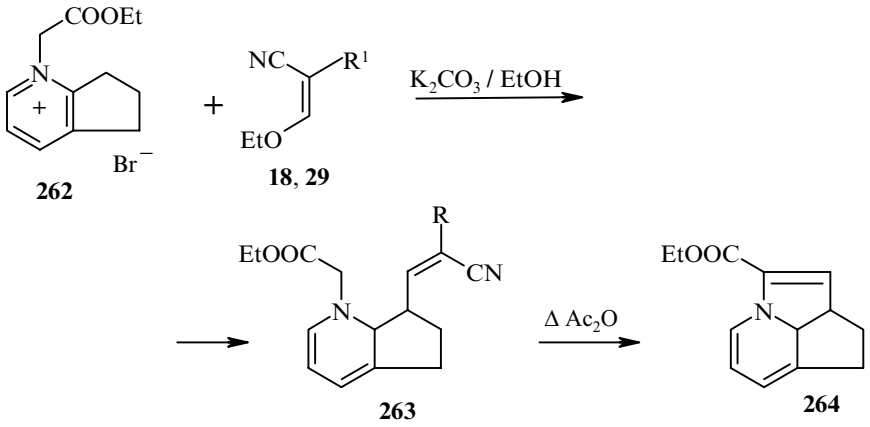


R = CN, COOEt; R^1 = $PhSO_2$

In the reaction of triazolium bromide **257** with ethoxyethylenes **258** and di(methylthio)ethylene **249** in the chloroform–alcohol medium in the presence of potassium carbonate the products **259** and **260** are formed with yields of 20-80% and 10-43% respectively. Under thermolysis conditions the reaction takes place with recyclization to triazine **261** [92]:

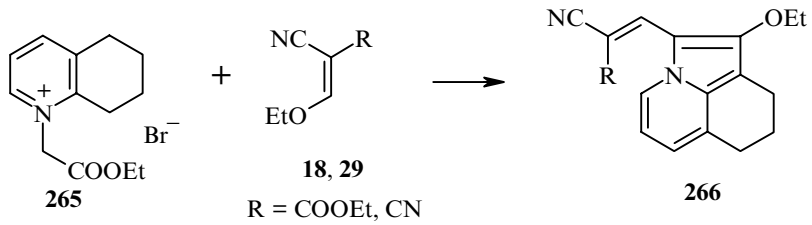


The reaction of 1-ethoxycarbonylmethyl-2,3-trimethylenepyridinium bromide (**262**) with unsaturated nitriles **18** and **29** under the influence of potassium carbonate leads *via* the generation of the anhydro base to the formation of the substitution products **263** with yields of 41-63%. The cyclization of the products by boiling in acetic anhydride is accompanied by a retro-Michael reaction with the formation of compound **264**, which exhibits antiallergic activity [93]:

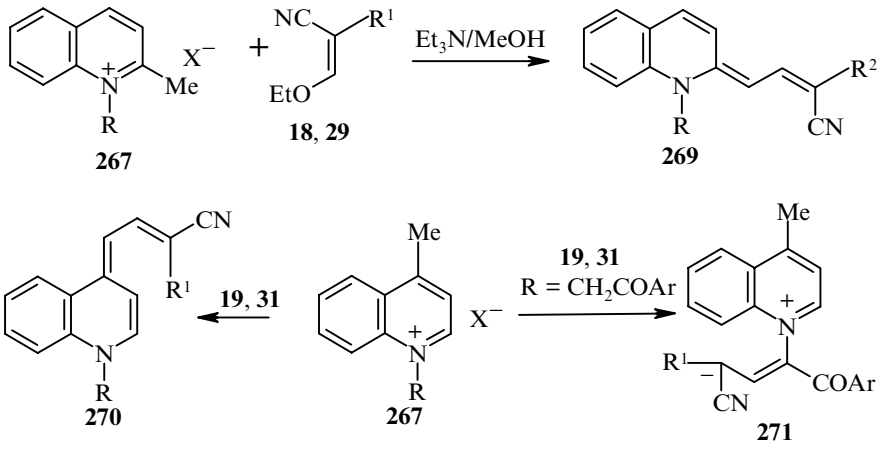


R = Ac, 4-Y-$C_6H_4COCH_2$ (Y = H, Me, Ph, Cl, Br);
R^1 = COOEt, CN

In contrast to salt **262** 1-ethoxycarbonylmethyl-5,6,7,8-tetrahydroquinolinium bromide (**265**) undergoes cyclization to compound **266** comparatively readily:



Merocyanines obtained by the reaction of 2- and 4-methylquinolinium salts **267** and **268** with ethoxymethylenecyano derivatives **18** and **29** have been described. In the case of 2- and 4-methylquinolinium salts only merocyanines **269** are formed with good yields as substitution products (through the anhydro base), but with 4-methylquinolinium (R = CH_2COAr) salt a mixture of merocyanines **270** and zwitterions **271** with a preference of **270** is formed [94, 95]:

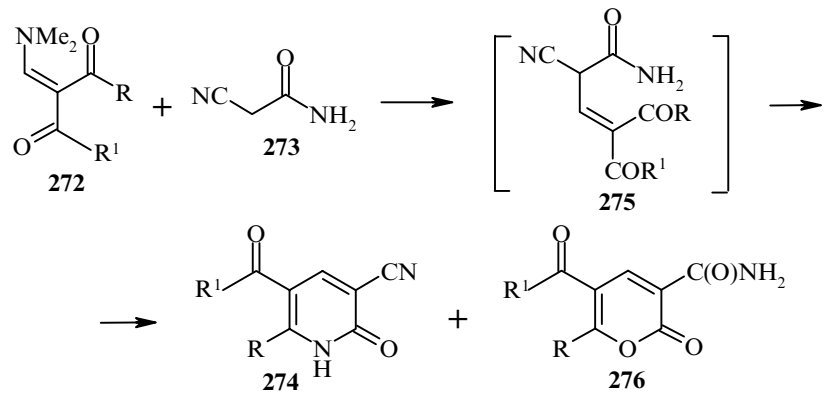


R = Alk; R^1 = CN, COOEt, CONHAr; X = Br, I

8. REACTIONS OF CYANOACETAMIDES AND CYANOTHIO- AND CYANOSELENO-ACETAMIDES

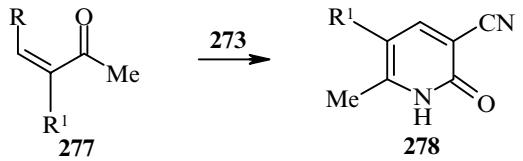
The reaction of functionally substituted ethylenes with cyanoacetamides and cyanothio- and cyanoselenoacetamides leads to the formation of 3-cyanopyridinechalcogenones – a prospective new type of organic compounds in the search for biologically active substances [96, 97]. The key stage of the formation of the heterocycles in this case can take place in two competing directions, i.e., nucleophilic substitution or Knoevenagel condensation, which under certain conditions affects the structure of the final product.

The reaction of dimethylaminomethylene derivatives **272** with cyanoacetamide **273** in the MeOH/MeONa or NaH/THF system at 20°C gave the corresponding 3-cyanopyridine-2(1H)-ones **274**, which are intermediate products in the synthesis of cardiotonic preparations [98-104]. In ethanol with metallic sodium the reaction gave a mixture of pyridones **274** and the products from cyclization of the hydrolyzed intermediate **275**, i.e., pyranones **276** [105]. Here the formation of compound **274** is preferred:



R = Me, Et, Bu, Ph; R^1 = Me, Et, Bu, Ph, Ar; $R^1+R^2 = (CH_2)_3$

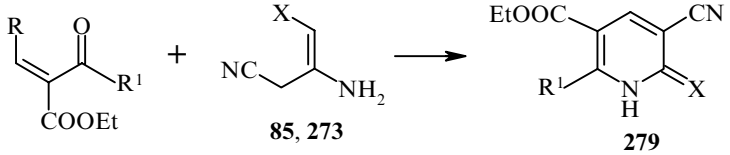
With ethoxyethylenes [106-108] or isopropylethylenes **277** [109] and cyanoacetamide **273** under analogous conditions pyridines **278** were obtained with yields in the order of 72%:



277 **278**

R = EtO, Me_2CH; R^1 = Me, COOEt, Ac, $C(O)OCH_2Ph$, imidazol-1-ylcarbonyl

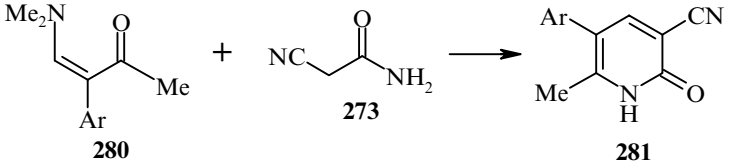
When cyanoacetamide and cyanothioacetamide were used in the reaction, pyridinones and pyridinethiones **279** were obtained with yields of 41-58%. Inhibitors of dihydrophospholatereductase and cell growth were synthesized from them [110, 111]:



85, **273** **279**

R = Me_2N, EtO; R^1 = Me, CH_2OEt, Ph, Het; X = O, S

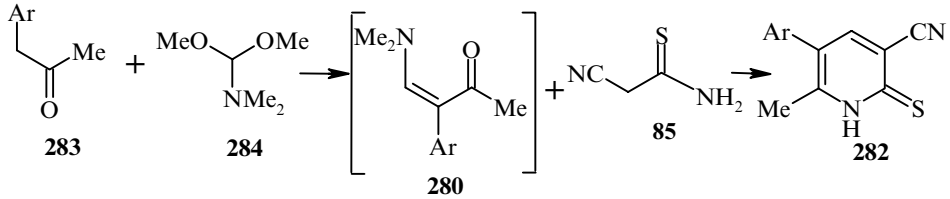
Pyridones **281**, which have biological activity, were synthesized by the reaction of substituted 1-acetyl-2-dimethylaminoethylenes **280** with cyanoacetamide **273** in methanol in the presence of sodium methoxide (or in the NaH/DMF or MeOH/DMF systems). They can be used as synthons for the production of cardiotonic preparations [112-119]. During the reaction of compounds **280** with cyanoacetamide in acetonitrile in the presence of potassium carbonate and tributylammonium hydrosulfate the products used for the treatment of asthma, thrombosis, hypertension, and heart failure were obtained [120]:



280 **273** **281**

Ar = 4-(imidazol-1-yl)phenyl, 4-pyridyl, 1H-imidazolyl-1-phenyl, 1H-benzimidazolyl-1-phenyl, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 3-$NO_2C_6H_4$, 3-$MeOC_6H_4$, 3-HOC_6H_4, thiazol-5-yl, 2-Me-5-thiazolyl, 4-Me-5-thiazolyl, 4-Me-2-thiazolyl, 2-(imidazol-1-yl)pyrid-5-yl, $C_6H_4OCH_2CH(OH)CH_2NNC_6H_4OMe$-2

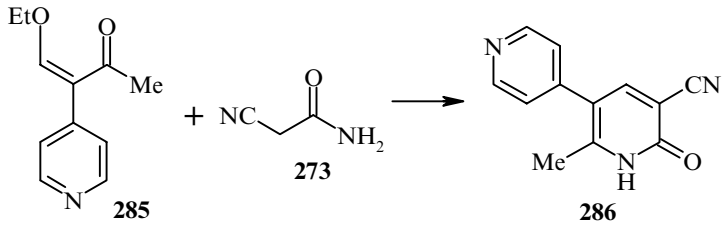
When cyanothioacetamide **85** was used in this reaction pyridinethiones **282**, which have cardiotonic and vasodilator activity, were obtained with yields of 57-81% [121]. Dimethylaminoethylene **280** was obtained *in situ* from arylacetone **283** and dimethylaminodimethoxymethane **284**:



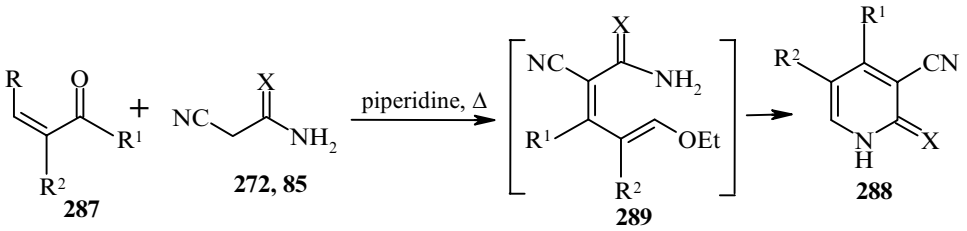
283 **284** **280** **85** **282**

Ar = Ph, pyrid-4-yl, 3,4-$(MeO)_2C_6H_3$

Pyridone **286** – the precursor of cardiotonic preparations – was obtained under analogous conditions using ethoxyethylene **285** [122]:

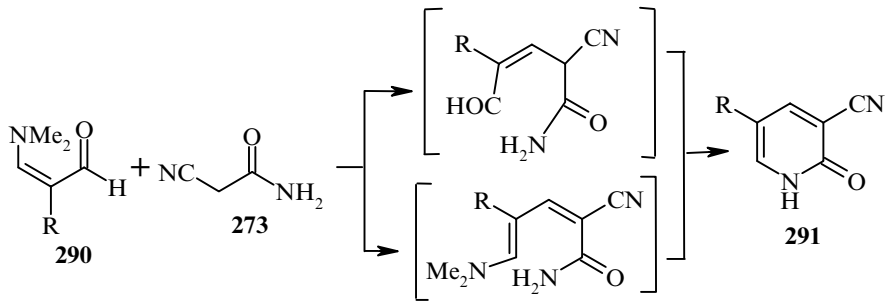


The reaction of ethoxyethylene **287** with cyanoacetamides and cyanothioacetamides **273**, **85**, which takes place at the key stage as Knoevenagel condensation, has been described. 4-Substituted pyridinones (pyridinethiones) **288** were obtained with yields of 40-55% by boiling in absolute ethanol in the presence of piperidine for 3 h [123, 124]. Here, the cyclization of the adduct **289** clearly takes place by mechanism of nucleophilic substitution.



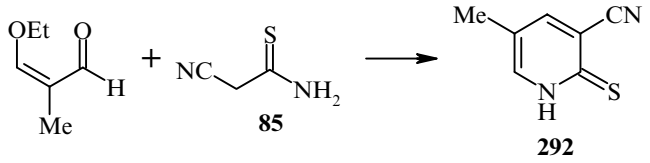
R = EtO, Me_2N; R^1 = Ph, $BzCH_2$, Me; R^2 = CN, COOMe, COOEt, Ac, Bz;
$R^1 + R^2 = (CH_2)_3$; X = O, S

The reaction of aryl- and heteroaryl-substituted 1-formyl-2-dimethylaminoethylenes **290** with cyanoacetamide **273** in the MeOH/MeONa system gave 3-cyano-2(1H)-pyridinones **291**, which exhibit cardiotonic activity or are used in the synthesis of the specific products [125-130]. It is worth mentioning that the structure of the final product **291** in this reaction does not depend on the key stage of the process.

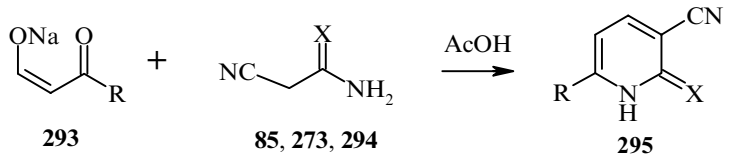


R = Ar, Het

The use of cyanothioacetamide **85** in the similar reaction led to pyridinethione **292**, which is an intermediate in the synthesis of a product exhibiting activity against a wide range of tumors in tests on mice [131]:

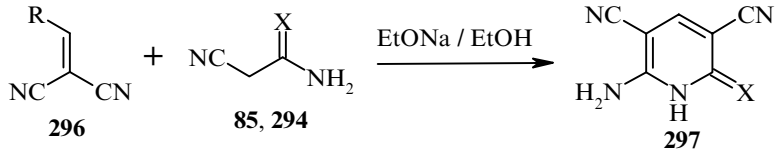


During treatment of sodium salt of 3-(adamantyl-1)-1-hydroxyprop-1-en-3-one (**293**) with the cyano derivatives of acetamide, thioacetamide, or selenoacetamide **294** in alcohol in the presence of acetic acid 6-(adamantyl-1)-3-cyanopyridine-2(1H)-one or the corresponding thione or selenone **295** were obtained with yields of 33-52% [132-136]:



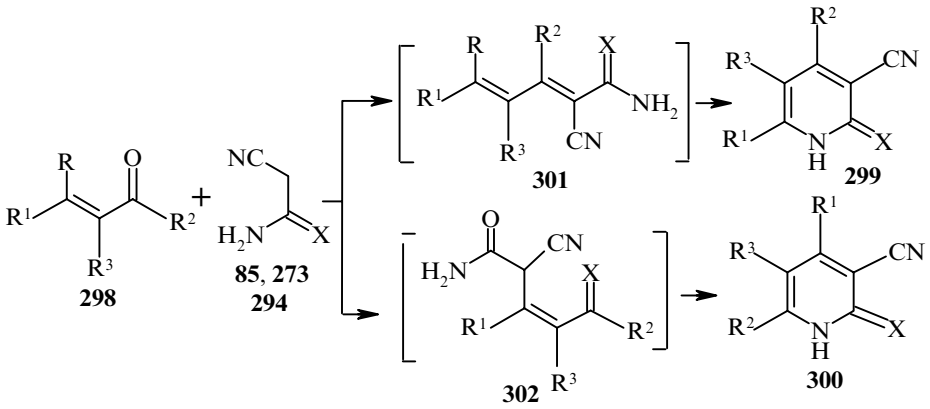
R = adamantyl-1; X = O, S, Se

The cyclization of nitriles **296** with cyanoacetamides and cyanothio- and cyanoselenoacetamides in the presence of 1 eq. of sodium ethoxide or N-methylmorpholine followed by acidification gave 6-amino-3,5-dicyano-2(1H)-pyridinones and the corresponding thiones and selenones **297** with yields of 67-80% [137, 138]:



R = EtO, NHPh, Ph; X = S, Se

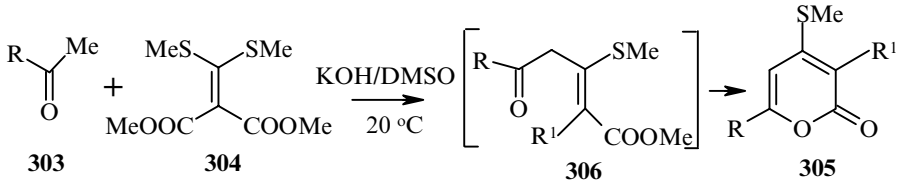
The reaction of functionally substituted ethylenes **298** with cyanoacetamides, cyanothioacetamides, and cyanoselenoacetamides, leading to the formation of the products **299** [139, 140] and **300** [141-147], has been described. Substances with cardiotonic activity were found among the products [148]. The products are probably formed *via* the corresponding intermediates **301** and **302**:



R = morpholin-4-yl, piperidin-1-yl, Me_2N, NaO; R^1 = H, Me, CF_3, Ph; R^2 = OEt, Ph, Ar, NHPh; R^3 = H; $R^2 + R^3 = (CH_2)_4$, $(CH_2)_5$; X = S, Se, O

9. REACTIONS OF OTHER ALIPHATIC, AROMATIC, AND HETEROCYCLIC CH ACIDS

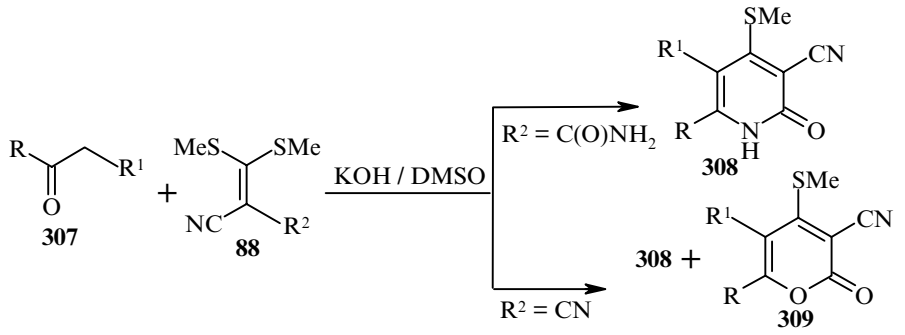
The reaction of ketones **303** with dimethyl di(methylthio)methylenemalonate **304** in DMSO in the presence of potassium hydroxide at 20°C for 8-10 h leads to a mixture of pyranones (mostly **305** (R^1 = COOMe)) and their hydrolysis and decarboxylation products **305** (R^1 = H) [149]. During the reaction the nucleophilic center of the methyl group of ketone **303** is probably activated by the action of the base and attacks the carbon atom at the double bond of the methylthiomethylene fragment of compound **304** with the formation of the substitution product **306**:



303 **304** **306** **305**

R = Ph, Ar; R^1 = COOMe, H

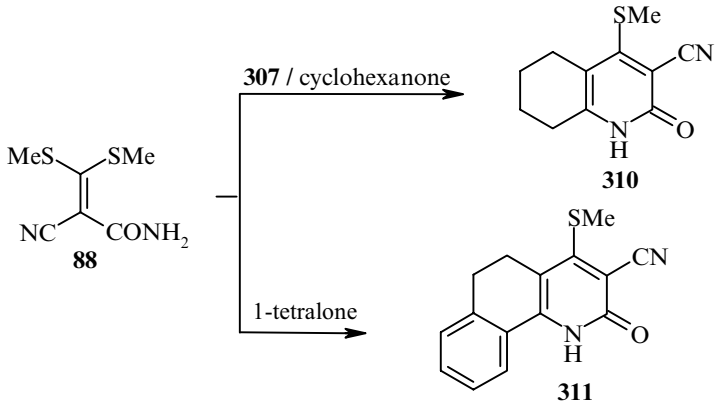
Under analogous conditions di(methylthio)methylene derivatives of cyanoacetamide **88** in reaction with the substituted methyl ketones **307** form the corresponding 2-pyridinones **308** with yields of 26-50%. With compound **88** where R^2 = CN pyranones **309** (yield 35%) were isolated in addition to pyridones **308** (yield 50%) [150]:



307 **88** **308** **309**

R = Me, $(CH_2)_2$COOH, Ph, Ar; R^1 = Me, COOEt; R^2 = C(O)NH_2, CN

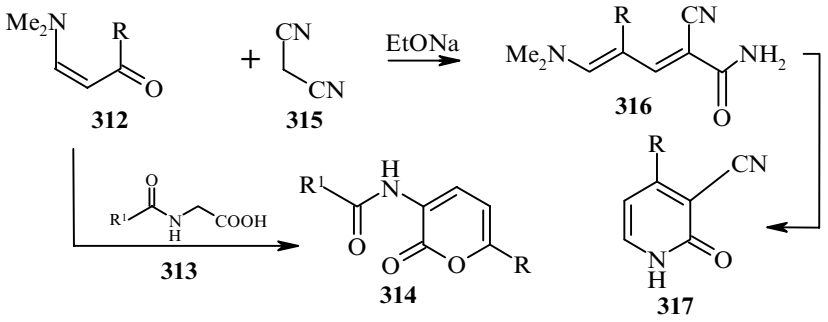
Tetrahydroquinolin-2(1H)-ones **310** were obtained in the reaction of compounds **88** (R^2 = C(O)NH_2) with ketones **307** in cyclohexanone, and dihydrobenzoquinolones **311** were obtained in the reaction of compound **88** with 1-tetralone:



88 **310** **311**

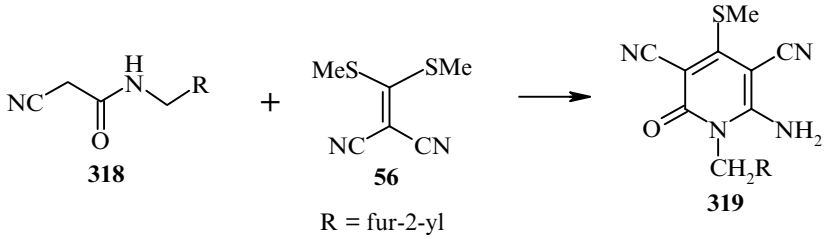
R = Me, $(CH_2)_2$COOH, Ph, Ar; R^1 = Me, COOEt

The reaction of dimethylaminoethylene **312** with N-acyl- or N-benzoylglycines **313** gave 2H-pyran-2-ones **314**. Amide **316** is formed in the reaction of compounds **312** with malononitrile **315** in the presence of a base. As a result of cyclization by boiling in acetic acid the amides **316** are converted into 1,2-dihydropyridin-2-ones **317** [151]. It should be noted that the key stage in the last reaction is condensation of the Knoevenagel type, whereas in the first, to judge from the structure of the product **314**, cyclization is preceded by nucleophilic substitution:



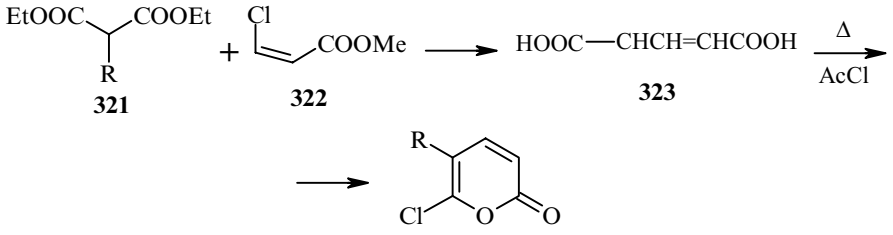
R = Ph, Het; R^1 = Me, Ph

In reaction with dimethylthiodicyanoethylene **56** N-furfuryl-substituted cyanoacetamide **318** forms pyridin-2-one **319** [152]:



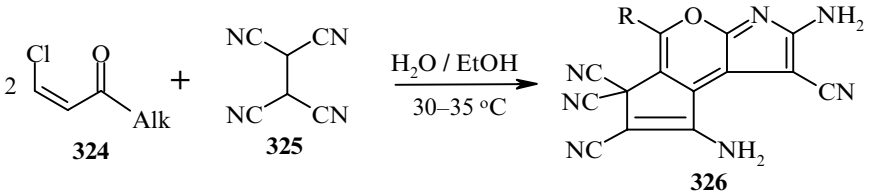
R = fur-2-yl

To investigate the structure–reactivity relationship in the series of 6-substituted 2-pyranones **320** as inhibitors of α-chymotrypsin these compounds were obtained from the α-substituted derivatives of malonic ester **321** and methyl β-chloroacrylate **322**. The reaction was conducted in THF at 80°C in the presence of sodium hydride, and the reaction mixture was then boiled with sodium hydroxide for 8 h. The substitution product **323** was isolated and underwent cyclization when heated in acetyl chloride in a sealed tube at 100°C for 12 h [153]:

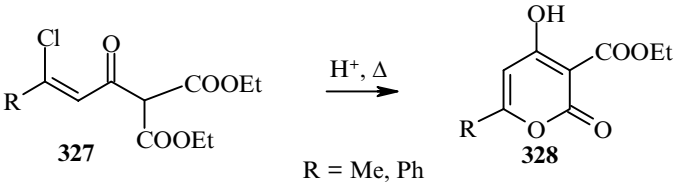


R = Bu, Ph, naphth-2-ylmethyl

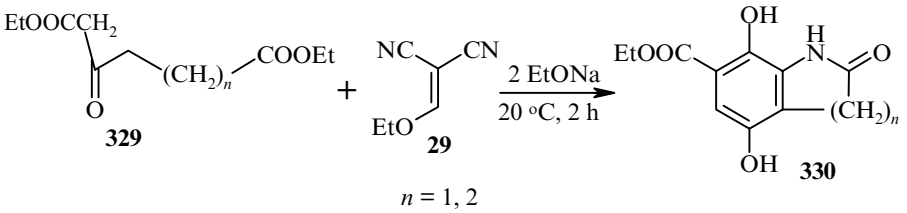
Nucleophilic substitution in β-chlorovinyl ketones **324** under the influence of tetracyanoethane **325** (aqueous alcohol, 30°C, 3 h) has been described. Condensed pyrans **326** were obtained with yields in the order of 60% [154]:



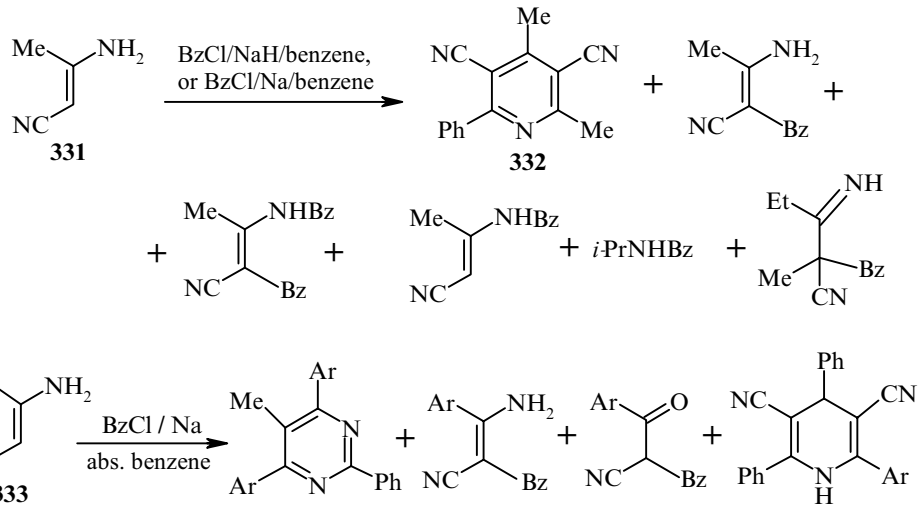
The intramolecular cyclization of esters **327** by a nucleophilic substitution mechanism, leading to derivatives of fulvinic acid **328**, is well-known. It takes place on boiling in an acidic medium [155]:



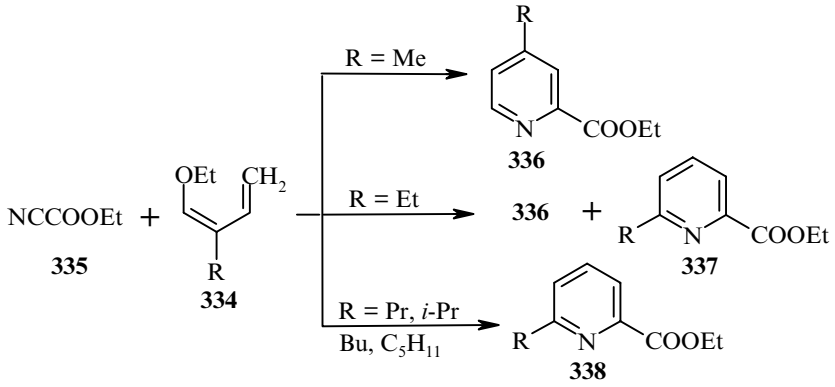
The reaction of ethoxymethylenemalononitrile **29** with diethyl 3-oxoalkanedicarboxylates **329** in the presence of sodium ethoxide at 20°C for 2 h leads to the condensed heterocycles **330** [156]:



The benzoylation of β-enamino nitrile **331** in the presence of sodium hydride in benzene leads mainly to pyridine derivative **332**. The same reaction, catalyzed by sodium powder, leads to a mixture of six different products, which can be separated by chromatography. Similarly, as a result of successive treatment with powdered sodium (absolute benzene, 60°C, 2 h) and BzCl (absolute benzene, 0-20°C, 10 h) unsaturated nitrile **333** forms a mixture of four products [157]:

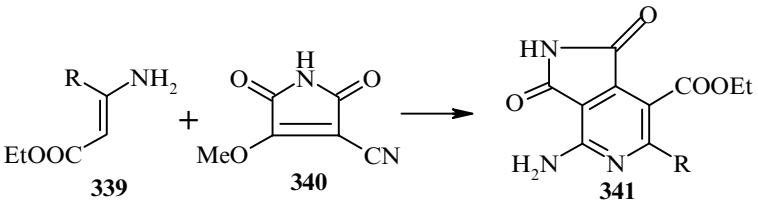


One of the paths to the synthesis of pyridines is [4+2]-cycloaddition involving the CN group as dienophile. Thus, the reaction of ethoxydivinyl **334** with nitrile **335** in the presence of cyclopentadienylcobalt cycloocta-1,5-diene as catalyst gave 4- and 6-substituted derivatives of 2-ethoxycarbonylpyridines **336-338** with yields in the order of 55% [158]:



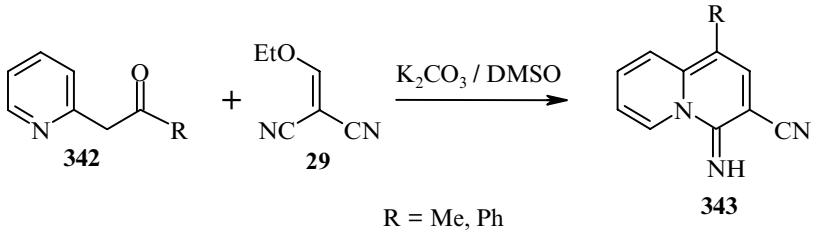
335 **334** **336** **337** **338**

Imides of 6-R-2-amino-5-ethoxycarbonylpyridine-3,4-dicarboxylic acids **341** were obtained by the reaction of substituted β-aminoacrylic acids **339** with 2-cyano-3-methoxymaleimide (**340**) [159]:



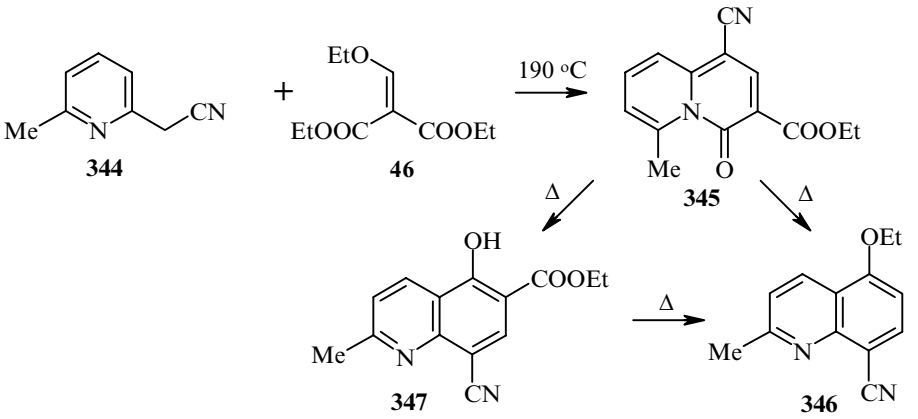
339 **340** **341**

The reaction of acetyl- and benzoylmethylpyridines **342** with ethoxymethylenemalononitrile **29** in DMSO in the presence of potassium carbonate gave quinolizines **343** with yields of 70 and 96% respectively [160]:

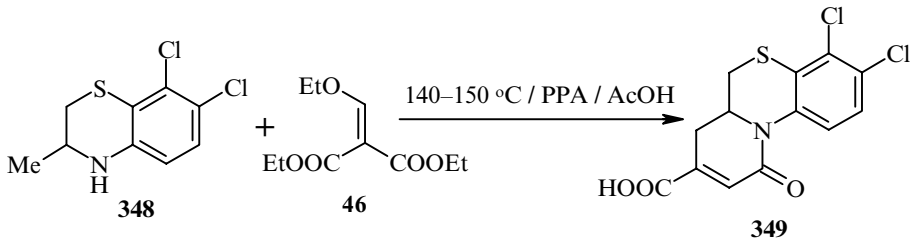


342 **29** **343**

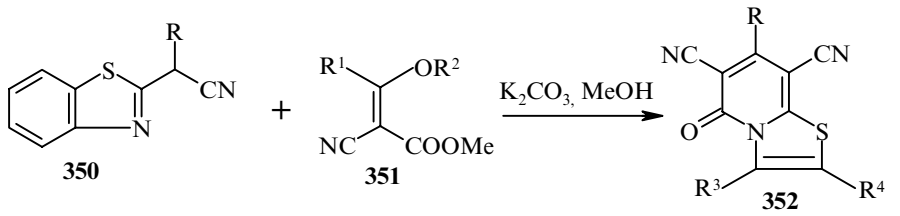
When 2-cyanomethyl-6-methylpyridine (**344**) was heated with ethoxymethylenemalonic ester **46** at 190°C, quinolizine **345** was formed. On further heating to 250°C it was converted into quinolines **346** and **347** [161]:



The reaction of 2,3-dihydro-4H-benzothiazine **348** with ethoxymethylenemalonic ester **46** at 140-150°C for 2 h led to pyrido[1,2,3-*d*,*e*][1,4]benzothiazine-6-carboxylic acid **349**, which is a precursor of antibacterial agents [162]:

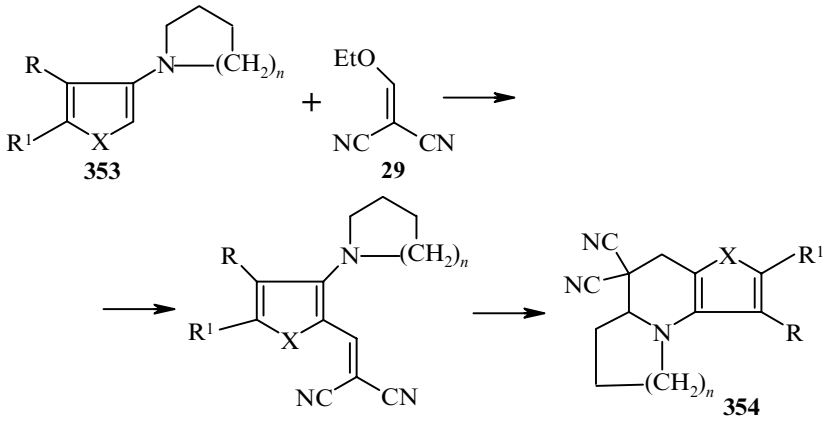


In reaction with alkoxyethylenes **351** in methanol in the presence of potassium carbonate 2-substituted benzothiazoles **350** gave 60-70% yields of the thiazole derivatives **352**, which are intermediates in the synthesis of dyes [163]:



R = CHC_6H_4Me-4, CHC_6H_4OMe-4; R^1 = H, Alk, Ph, Ar; R^2 =Me, Et; R^3+R^4 = CH=CH–CH=CH

When boiled with methoxymethylenemalononitrile **29** in butanol for 35-48 h furans and thiophenes **353** are converted into the corresponding tricyclic systems **354** with yields of 80-93% [164]:



R = Alk, Ph; R^1 = Alk, Ph; R+R^1 = benzo; X = S, O; *n* = 1, 2

Analysis of the data on the use of vinyl substitution reactions in the synthesis of heterocycles demonstrates the strong synthetic potential and the prospects of these reactions in the development of controlled methods for the synthesis of polyfunctional heterocyclic systems and their annellated analogs, which possess a broad range of biological activity.

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