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Functionally-substituted Alkoxyethylenes in Reactions with Nucleophiles. Part I. Synthesis of Six-membered Heterocycles

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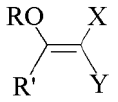
Contents

I. INTRODUCTION

Nucleophilic vinyl substitution is an extensively developing field of organic chemistry providing a possibility to prepare enormously versatile heterocyclic systems among which quite a number possess biological activity as outlined in reviews [1–4]. Therewith the numerous data published within the last decade on the reactions of functionally-substituted alkoxyethylenes (hereinafter AOE) with nucleophilic reagents have not even independently considered and require systematization and generalization. The general formula of AOE under consideration is



where R = Alk; R' = H, Alk; X and Y are electron-withdrawing groups.

These compounds can be classed within a single group basing on the general method of preparation thereof. Both on the laboratory and industrial scale they are mostly prepared by reaction between CH-acids and orthoesters, usually triethyl orthoformate (TOF). Therewith ethoxymethyene derivatives of the CH-acids are obtained.

Note that in this review are not considered compounds containing the alkoxy group attached at the double bond when R' ≠ H, Alk and also X, Y = H, Alk, Hal. The latter compounds are qualitatively dissimilar classes of substances that differ as a rule not only in the chemical properties but also in the preparation procedures as described in [5–11].

The following functionally substituted AOE are the most often used in syntheses: diethyl ethoxymethylenemalonate (EMME, **1**), dimethyl ethoxymethylenemalonate **2**, ethoxymethylenemalononitrile (EMMN, **3**), ethyl ethoxymentylenecyanoacetate (EMCA, **4**), ethoxymethylene derivative of Meldrum's acid **5**, methoxymethylene derivative of Meldrum's acid **6**, ethoxymethyleneacetylacetone **7**, 2-ethoxymethylene-1-phenyl-1,3-butanedione (EMPB, **8**), and some others.

A good nucleofuge, alkoxy group, is attached to the double bond of AOE; therefore the best examined reaction of these compounds is nucleophilic vinyl substitution (S_NVin) of the alkoxy group affording a replacement product which as a rule undergoes cyclization involving one of electron-withdrawing groups of the initial AOE. Besides the AOE can enter into cycloaddition by their double C=C bond and also can play the role of their own precursors, orthoformates, i.e. under certain conditions they can transfer the methylene group. It should be noted also that the ethoxymethylene derivatives of unsymmetrical CH-acids can exist as *Z*- and *E*-isomers (**4, 7, 8**). However in most publications the use of one

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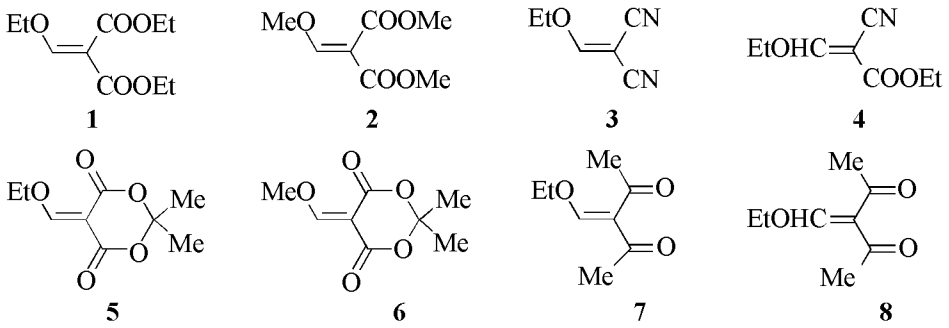
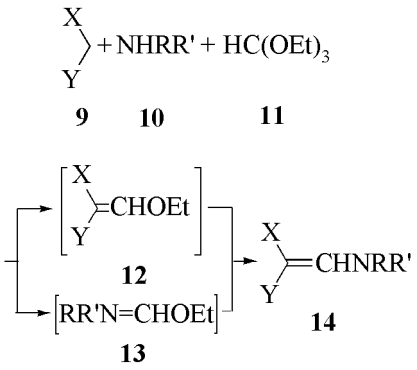


1 **2** **3** **4**

5 **6** **7** **8**

or another isomer was not indicated; therefore we mentioned the exact isomer only in some cases in this review.

AOE may be used both as initial compounds and as nonisolated intermediates. The latter syntheses are three-component condensations of CH-acid **9**, amine **10**, and TOF **11**, where TOF is a supplier of the methylene component closing the chain between the methylene-active carbon and nitrogen. These reactions essentially may with equal probability proceed via formation of amine ethoxymethylene derivatives **13**, or through AOE **12** that are the subject of the present review.



9 **10** **11**

12 **13** **14**

Note that the yield of enamine **14** prepared in a three-component system is frequently significantly higher then the yield in a two-component synthesis from specially prepared AOE **12** and amine **10**.

II. SYNTHESIS OF SIX-MEMBERED HETEROCYCLES

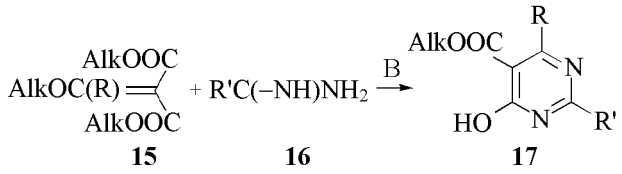
II.1. *Pyrimidines*

The general strategy of pyrimidine synthesis includes several versions distinguished by the structure of the combined fragments. In the AOE chemistry almost always is used the method of condensing a unit of three carbon atoms C–C–C with a fragment N–C–N that results directly in the pyrimidine ring. This procedure is valuable for it is generally suitable for application to the synthesis of versatile pyrimidine derivatives.

Reactions of CH-acids alkoxymethylene derivatives containing an equivalent of aldehyde group are used in the syntheses of pyrimidines unsubstituted in *4* position, and at the use of CH-acids 1-alkoxyalkylidene derivatives (containing an equivalent of a keto group) pyrimidines with substituents in 4 position are obtained.

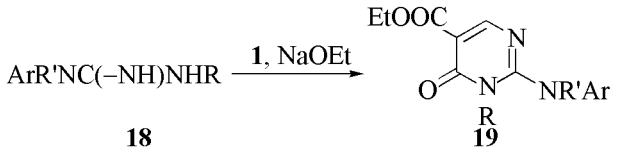
For instance, the treatment with AOE **15** of salts of N-unsubstituted amidines **16** afforded as the prevailing tautomers 4-hydroxypyrimidines **17** [12–16], and with arylguanidines 18 arose 6-oxo-1,6-dihydropyrimidines **19** [16]. Compounds **17** may be used as fungicides, insecticides, and acaricides, and the hydrolysis products of pyrimidines **19** exhibit high antiallergic activity combined with low toxicity. R = H, Me; R' = H, Me.

Cyclization of olefin **2** with substituted amidines **20** furnished in good yield a single product, pyrimidones **22**. At the application to this process of dimethyl methoxyethylidenemalonate **15a** a formation



15 **16** **17**

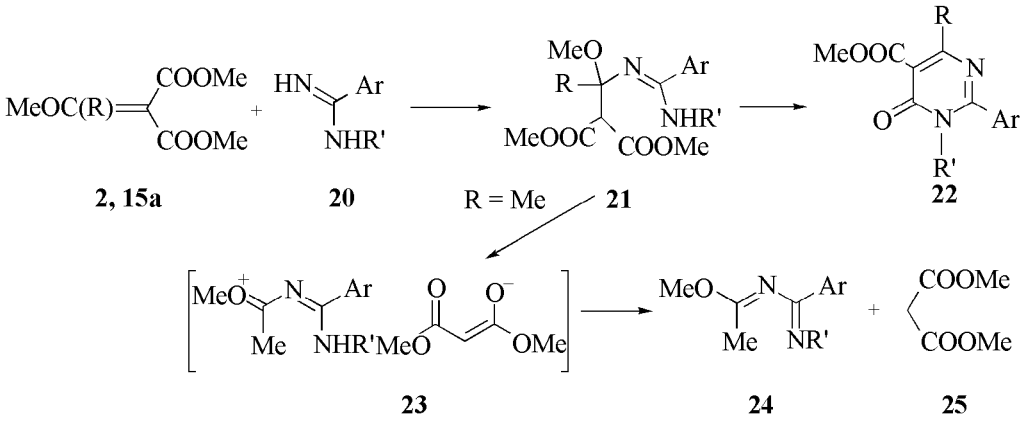
R = H. Alk; R' = H, Alk, AlkS, Ph, Ar, Het, CH_2CH_2OMe;
B = NaOH, KOH, NaOEt



18 **19**

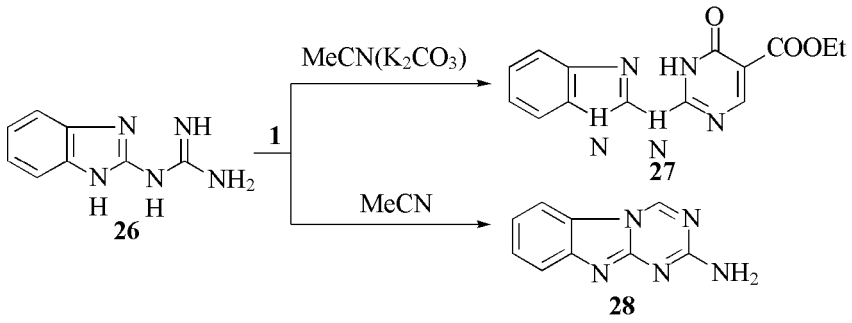
R = H, Me; R' = H, Me.

of acyclic product **24** was also observed, and depending on the substituents compound **24** could prevail in the product mixture. The latter compound arose due to steric hindrance in cyclization of the intermediate Michael adduct **21** caused by a substituent in position **4** and that attached to the nitrogen atom . In this case the prevailing direction of further reaction is fragmentation of structure **21** through oxonium salt **23** resulting in compound **24** and dimethyl malonate **25** [17].



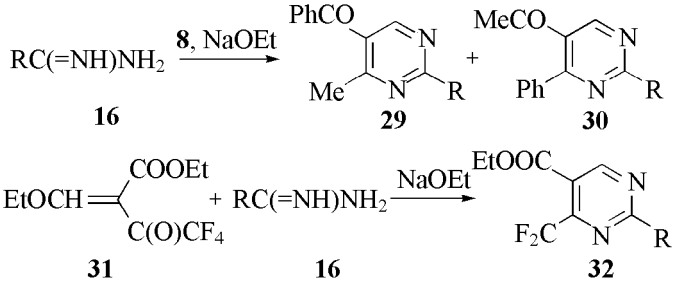
R = H, Me; R' = H, Me, $CH_2CH_2(OMe)_2$.

The boiling of amidine **26** with EMME in MeCN in the presence of K_2CO_3 gave rise to pyrimidine-4-(3*H*)-one **27**, and without K_2CO_3 a fused symm-triazine **28** was obtained [18]. Thus in this reaction the AOE plays the role of methylene group transmitter; this ability is often used for closing the ring with a methylene bridge between two nitrogen atoms. Note that tricycle **28** is a potential anti-AIDS agent.



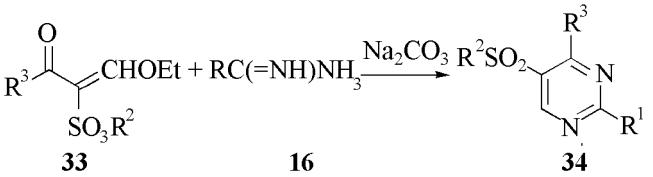
The cyclocondensation of EMPB with amidine hydroiodides **16** in the presence of NaOEt/EtOH afforded isomeric pyrimidines **29** and **30** [19, 20]. At the use in this reaction of ethyl trifluoroacetate ethoxymethylene derivative **31** the cyclization occurred exclusively at the trifluoroacetyl group providing pyrimidine **32** [21], and with AOE **33** formed 5-sulfonylpyrimidine **34** [22].

The application of three-carbon fragment containing a cyano group may be regarded as an important modification of the above general synthesis. The main advantage of the procedure consists in direct introduction of an amino substituent into position **4** or **6** of the pyrimidine ring. For instance, the reaction with salts of N-unsubstituted amidines **16** furnished 4-aminopyrimidines **35** [23], and the reaction with N-substituted amidines **36** in benzene afforded 4-imino-3,4-dihydropyrimidines **37**.



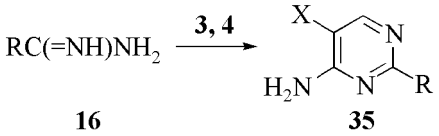
R = Me, Ph, NH_2, SMe.

It should be noted that carrying out the latter reaction in acetic acid afforded in 50% yield the product of S_NVin substitution of an ethoxy group with a nitrogen atom **38** [24].



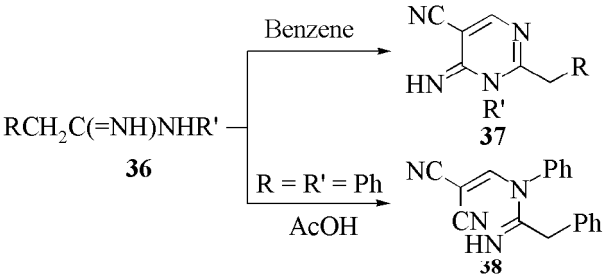
33 **16** **34**

R^1 = Ph, NH_2, $PhCH_2S$; R^2 = 4-Tol, Me; R^3 = Me, Ph.



16 **35**

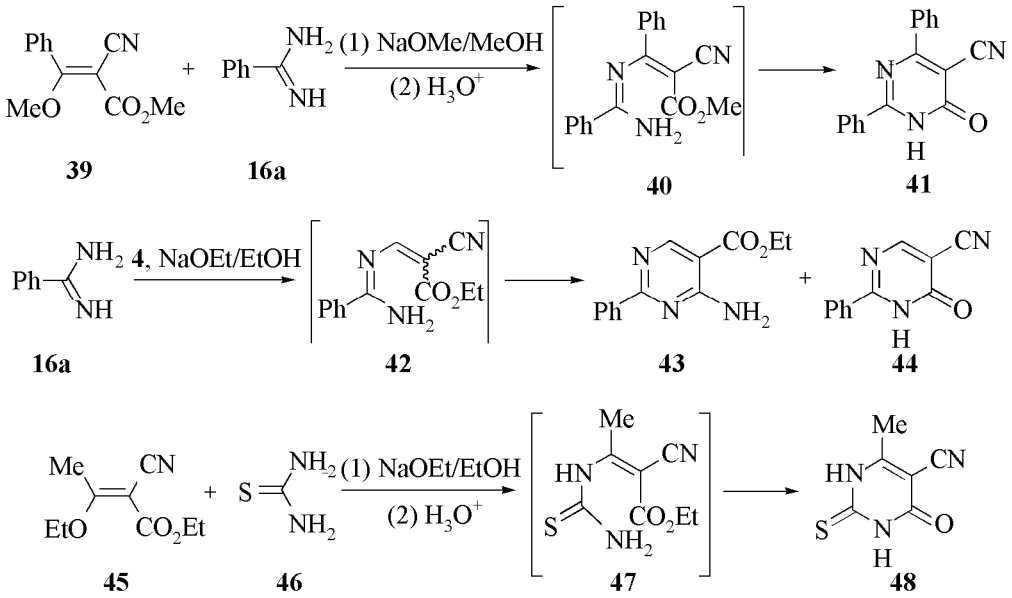
X = CN, COOEt; R = Ph, SAlk, SAr, cycloalkylthio; X = Br, I, Merrifield's peptide resin.



36 **37** **38**

R, R' = Ph, Ar.

The regioselectivity of cyclization of benzamidine **16a** and thiourea **46** with various AOE **4, 39, 45** was studied in [25], and it was revealed that the regioselectivity is affected by the geometry of the double carbon–carbon bond in intermediates **40, 42, 47**. Thus the steric hindrances arising between phenyl (methyl) group and the ethoxycarbonyl function result in the *Z*-configuration of intermediates **40** and **47** and consequently lead to cyclization at this group provid-



39 **16a** **40** **41**

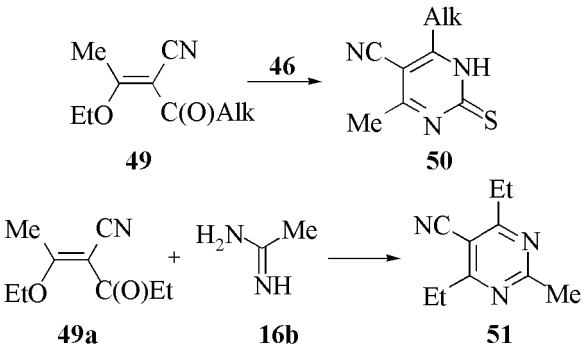
16a **42** **43** **44**

45 **46** **47** **48**

ing the corresponding 4-oxopyrimidines **41** and **48**. At the use of unsubstituted EMCA arose two possible pyrimidines, **43** and **44**.

Reaction of thiourea **46** and acetamidine **16b** with olefins of *Z*-configuration **49** and **49a** occurred at the keto group and afforded 5-cyanopyrimidines **50** and **51** [26].

The effect of substituents in diaminomethylenehydrazones **53** and **61** on the structure and yield of products in reaction with sterically hindered ethoxy-



49 **50**

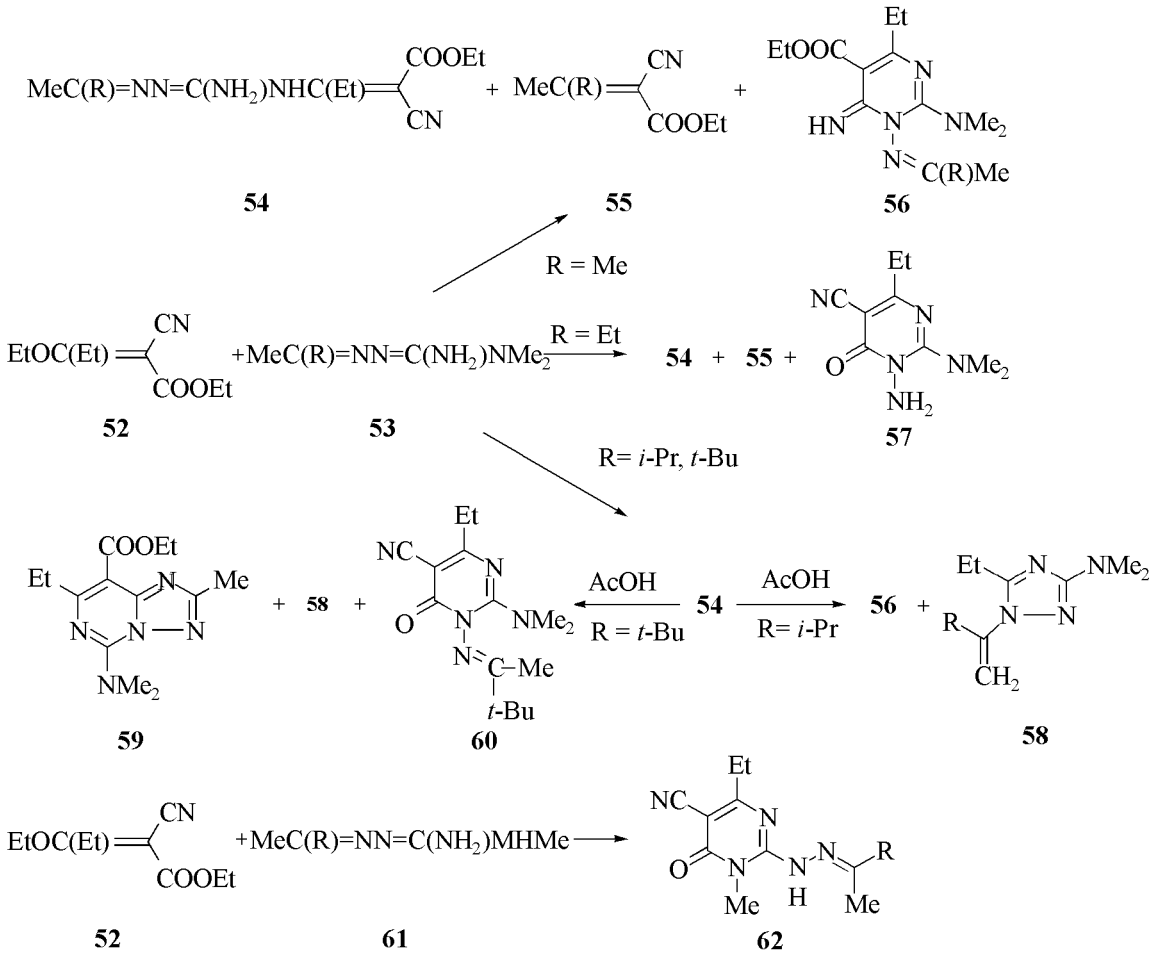
49a **16b** **51**

methylenecyanoacetate **52** was studied [27]. It was demonstrated that in reaction of olefin **52** with amine **53** arose in various ratios mixtures of conjugated systems **54, 55**, and 1,6-dihydropyrimidines **56, 57.**

From olefin **52** and amine **61** 1,6-pyrimidine-6-ones were obtained. The heating of amine **54** (R = *i*-Pr, *t*-Bu) in AcOH furnished a mixture of cyclic systems **56, 58–60**. The formation of alkene **55** deserves special attention: it can be represented as methylene components exchange between two CH-acids.

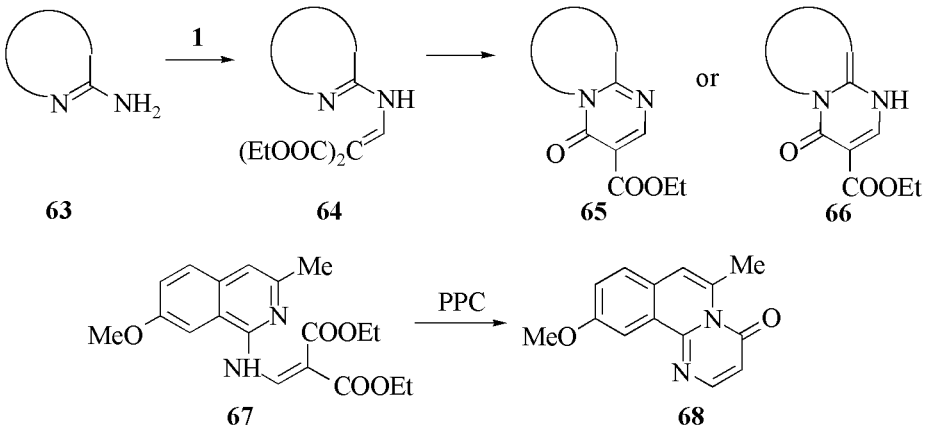
AOE are widely applied to syntheses of fused pyrimidines containing bridging nitrogen atom. As the nitrogen-containing fragment versatile heterocycles are used with an amino-group in the *ortho*-position to the endocyclic nitrogen **63**.

Although both nitrogen atoms might act as nucleophiles, it was demonstrated that at the first stage of the reaction (S_NVin) in majority of cases amino group was involved, and the reaction proceeded along Gold–Jacobs type through acyclic intermediates, CH-acids **64, 69**. The reaction with EMME in this

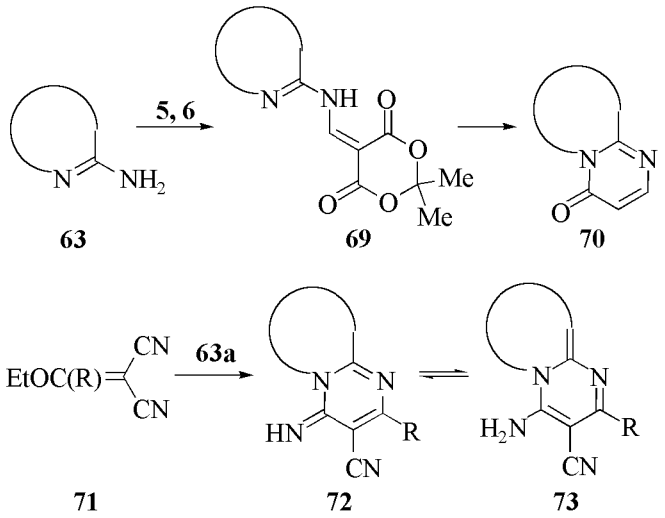


R = Et, *t*-Bu.

case occurs in one step (depending on the reagents either in solvents, EtOH, DMF, AcOH, or without solvents under microwave irradiation). If the product of S_NVin **64** was isolated, the further reaction conditions were varied in wide limits. Olefin **64** can cyclize at heating in diphenyl oxide, in polyphosphoric acid (PPA), in Dowtherm A, or in a pressure reactor affording fused 6-oxo(oxy)pyrimidines with an ethoxycarbonyl group in *5* position **65, 66** [28–46]. This group can be eliminated by treating **67** with PPA at 130°C, providing 3-unsubstituted pyrimido[2,1-a]isoquinolin-4-one **68** [40]. It was found that pyrimidines thus prepared exhibit antimicrobial, analgesic, antitumor activity, stimulate the central nervous system and possess antiandrogenic influence.

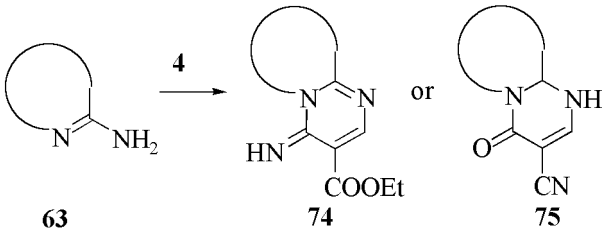


Meldrum's acid alkoxymethylene derivatives **5, 6** in this reaction cyclize to give fused 5-unsubstituted 6-oxopyrimidines **70** [41–43, 47], and EMMN derivatives **71** afford fused 4-amino(imino)-5-cyanopyrimidines **72, 73** [44, 48–53], that may be used as helminthicides, as filaricidal, leishmanicidal, and antiallergic medicines.



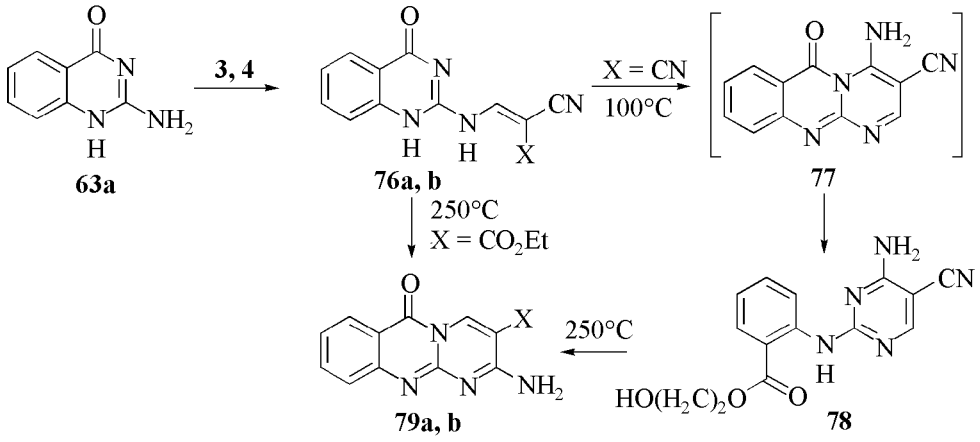
R = H, Me.

Unsymmetrical ethoxymethylene derivatives of ethyl cyanoacetate can undergo cyclization both at cyano and ethoxycarbonyl group affording respectively 5-ethoxycarbonyl- or 5-cyanopyrimidines **74, 75** [44–46, 52–54].



R = H, Me.

Somewhat different products arise in reaction of EMMN and EMCA with quinazoline **63a**, although the mechanism of reaction is the same. EMCA formed a stable product S_NVin (**76a**) that underwent

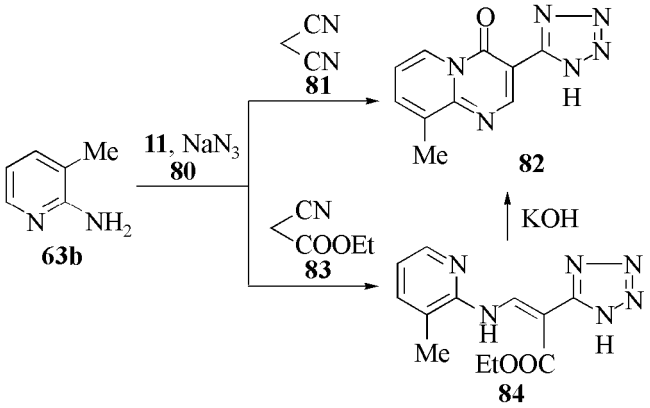


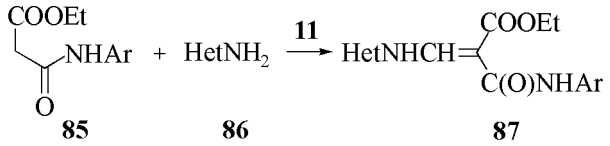
X = CO_2Et (**a**), CN (**b**).

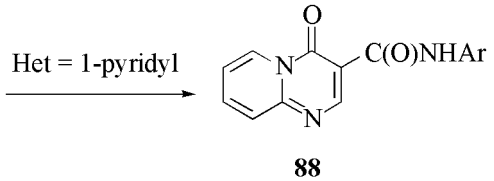
further cyclization at 240–270°C yielding pyrimido-[2,1-*b*]quinazoline **79a**. Intermediate **77** presumably arises in reaction of quinazoline **63a** with EMMN, but in this case under the reaction condition it reacts with a solvent molecule providing substituted ester of 2-(pyrimid-2-yl)aminobenzoic acid **78**. Pyrimidine **78** cyclizes into pyrimido[2,1-*b*]quinazoline **79b** that allows suggesting the same cyclization pathway also for compound **76a** [55].

Fused pyrimidines can be obtained also by one-pot process reacting CH-acids **81, 83**, 2-amino-3-picoline **63b**, TOF, and NaN_3 in AcOH. Cyanoacetate **83** formed in this reaction an intermediate product **84** which when treated with KOH furnished 4H-pyrido-[1,2-*a*]-pyrimidine **82**. The latter can be prepared by one-pot procedure if as CH-acid is used malononitrile **81** [56].

In one-stage three-component condensation of malonoanilic acids **85**, heterylamines **86**, and TOF acrylic acid arylamines **87** were obtained that at Het = 2-pyridyl cyclize in ethylene glycol, PPA, or acetic acid into pyrido[1,2-a]pyrimidine-3-carboxylic acid aryl amides **88** [57]. The latter may be used as antiphlogistic and analgesic drugs.

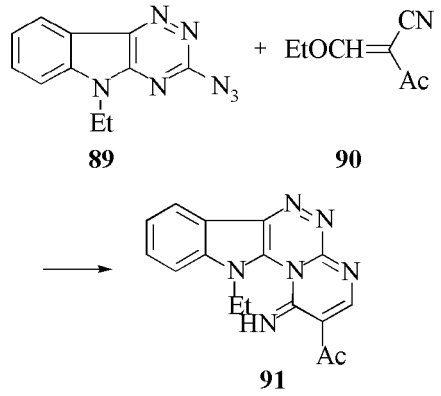






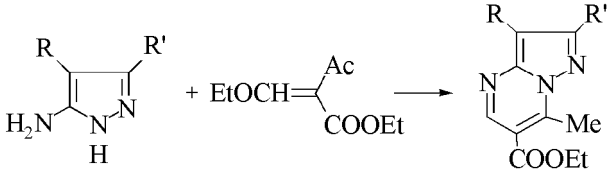
In the reaction of triazino[5,6-*a*]indole **89** with ethoxymethylene derivative of acetylacetonitrile **90** the cyclization takes place at cyano group furnishing fused 6-imino-1,6-dihydropyrimidine **91** [58].

Boiling of 5-aminopyrazole derivatives **63c** with AOE **92** afforded fused pyrimidines **93**, and from 4-phenyl-3-hydroxy-5-aminopyrazoles **63d** the expected product **94** was obtained in a mixture with 9-hydroxy-5-methyl-3-phenylpyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid **95** [59]. Note this relatively seldom example of S_NVin reaction at the endocyclic nitrogen atom



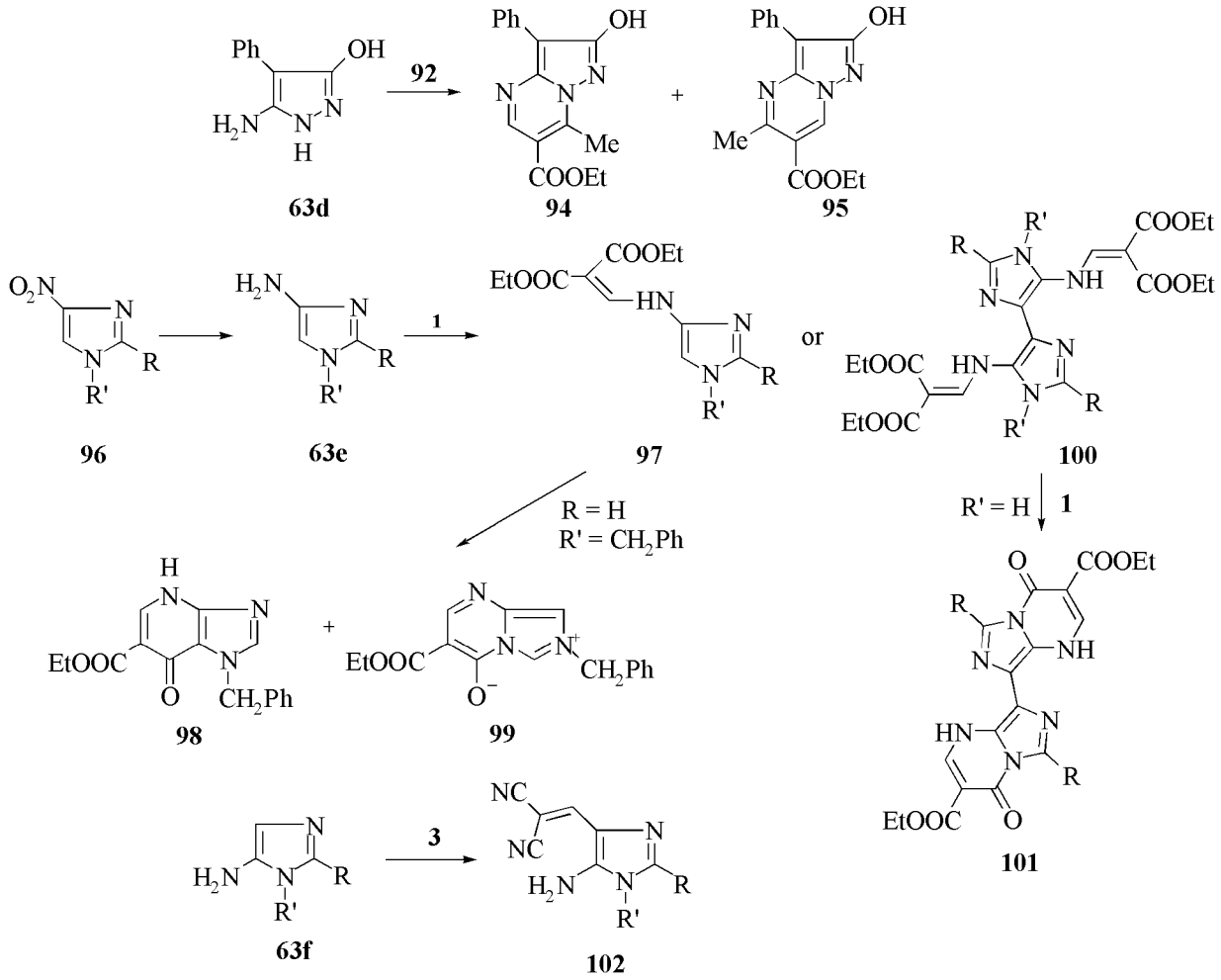
Het = 2-pyridyl, 4-pyridyl, 2,6-$(CH_3O)_2$-4-pyrimidyl, 4-antipyryl.

In the reaction of 4-aminoimidazole **63e** with EMME formed the expected product S_NVin **97** which under standard conditions (H_2SO_4, Ac_2O) underwent ring closure affording a mixture of two products: imidazo[4,5-*b*]pyridine **98** and imidazo[1,5-a]pyrimidin-2-ium-5-olate **99**. But when imidazoles **63e** are generated in situ in the presence of EMME the products are 5,5'-diimidazoles **100**. The latter undergo ring closure into imidazo[3,4-*a*]pyrimidines **101.** In contrast to the above reactions 5-aminoimidazoles **63f** react with EMMN affording in high yield (84%) products of C-substitution **102** [60].



R = H, Me, Ph, Het, CN, COOEt; R' = H, Alk, Ph, OH, Het.

The reaction of 3-amino-4-cyanopyrazole **63g** with AOE **103** was studied in [61], and it was found that in alcoholic solution formed intermediate **104** that further cyclized into 6-acetyl-3-cyano-7-ethoxycarbonylpyrazolo[1,5-*a*]pyrimidine **105**.

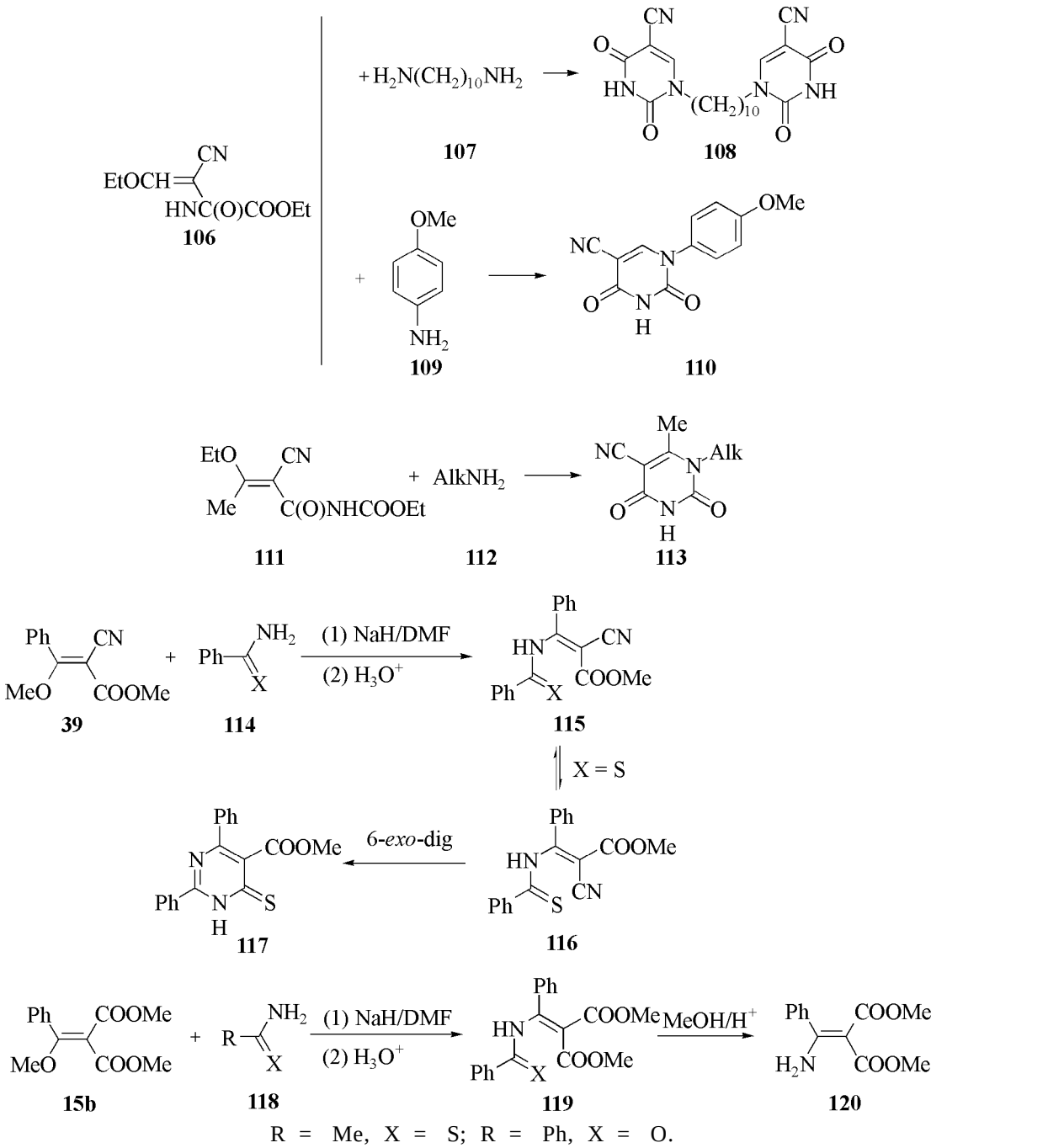


Pyrimidine syntheses based on combining fragments C–C–C–N–C and N have no general importance and are sometimes used in preparation of uracil derivatives. For instance, the reaction of enol ether **106** with diamine **107** in the presence of NaOH afforded system **108** [62], and with amine **109** pyrimidine **110** was obtained [63]. Olefin of Z-configuration **111** in reaction with amine **112** gave rise to pyrimidine **113** [64].

Pyrimidine synthesis where the source of one of the two nitrogens was a cyano group was described in [25]. The reaction of (thio)benzamide **114** with methyl 3-methoxy-2-cyano-3-phenylpropenoate **39** gave rise to alkene **115** whose *Z*-configuration was proved by X-ray diffraction study and NMR spectra.

Ring closure in structure **115** (R = S) in methanol involves inversion at the double carbon-carbon bond, an attack on the *sp*-hybridized carbon atom from the cyano group of **116**, and results in pyrimidinethione **117**. Regioselectivity of **117** formation is due to stereoelectronic factors. The rigidity of the backbone of **115** limited the mobility of terminal groups and

hampers the reaction. At the same time the attack of the cyano group from **116** involving formation of an angle of **120** by atoms SCN in **116** occurs without distortion of the chain. This pathway is proved by the fact that olefin **119** prepared from AOE **15b** and amide **118** at standard ring closure conditions (boiling in methanol) does not undergo cyclization, and at acidifying furnishes olefin **120**.



Thus in the synthesis of pyrimidine derivatives the AOE serve mainly as providers of three-carbon block C–C–C. The processes where the AOE furnish other fragments (C–C–C–N, C–C–C–N–C) are of particular character and are seldom used. The interest attracted by these pyrimidine preparation procedures originates from the fact that pyrimidine structures are present in numerous natural substances, and pyr-

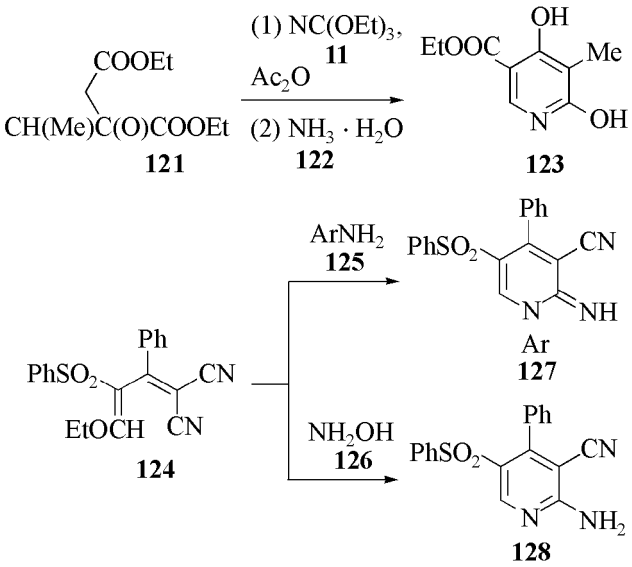
imidines proper frequently also possess biological activity.

II.2. *Pyridines*

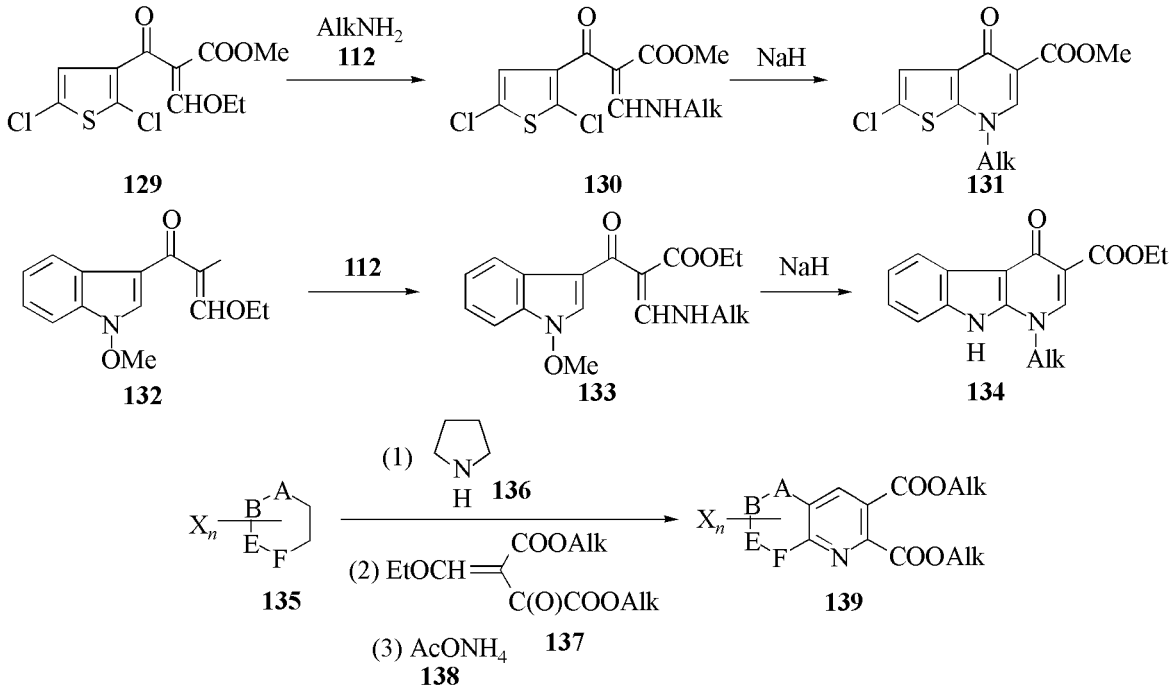
Among the syntheses of various heterocycles involving AOE those providing pyridines are the most diverse with respect to their methods and are more sophisticated. It is likely the reason why these reactions are now fewer in number (save the syntheses of substituted quinoline-3-caboxylic acids which exhibit a wide range of biological activity). The diversity of synthetic methods applied to preparation of pyridine derivatives is due to the possibility to build up the pyridine ring from various structural fragments and combinations of carbon and nitrogen atoms.

The simplest pyridine synthesis consists in reaction of 1,5-dicarbonyl compounds with ammonia. For instance, one-pot reaction of CH-acid **121** with acetic anhydride and triethyl orthoformate followed by treatment with 30% aqueous ammonia **122** afforded 2,4-dihydroxy-3-methyl-5-ethoxycarbonylpyridine **123** [65], an intermediate in the synthesis of antimicrobial pharmaceuticals.

An example of pyridine synthesis from compounds containing C_5-chain and ammonia derivatives is the treatment of AOE **124** with primary aromatic amine **125** or hydroxylamine **126** furnishing respectively 2-imino-1,2-dihydropyridines **127** and 2-aminopyridine **128** [66]. The reaction of AOE **129** and compound **132** with primary amines **112** resulted in its turn in S_NVin products **130** and **133** obtained as a mixture of *E*- and *Z*-isomers.



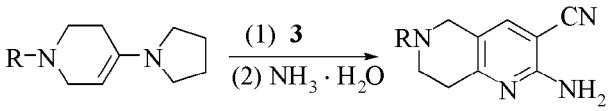
Cyclization of the latter effected under the action of NaH base in THF afforded respectively methyl thieno[2,3-*b*]pyridinecarboxylates **131** [67] and pyrido-[2,3-*b*]indoles **134** [68]. Thienopyridines **131** are characterized by appreciable antimicrobial activity.



One of A, B, E, F = O, S, SO, SO_2, NR_3, CO, CH; therewith the other atoms = C; X = Hal, Alk, AlkO, OH, CF_3, Ph, Ar, Het; *n* = 0–6.

A large series of various quinoline derivatives **139** used as efficient herbicides is prepared by reaction of six-membered tetrahydroheterocyclic derivatives **135** with pyrrolidine **136** followed by treatment with AOE **137** and ammonium acetate **138** [69].

Interleukin inhibitors **141** are prepared by reaction of tetrahydropyridine **140** with EMMN followed by treatment with ammonia [70].

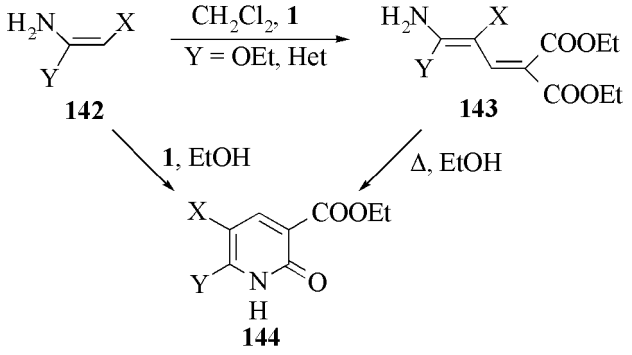


140 **122** **141**

R = C_6H_4CN, Ts.

In the AOE chemistry in pyridine syntheses the C_5 chain is usually built up from two or more fragments of carbon–carbon chain where one among them contains a nitrogen atom.

A chain is built from fragments C–C–C and C–C–N by several procedures. A three-carbon fragment is always present in AOE, and the C–C–N part may arise from linear enamine, CH-acid with an endocyclic nitrogen atom, or from aromatic amine.



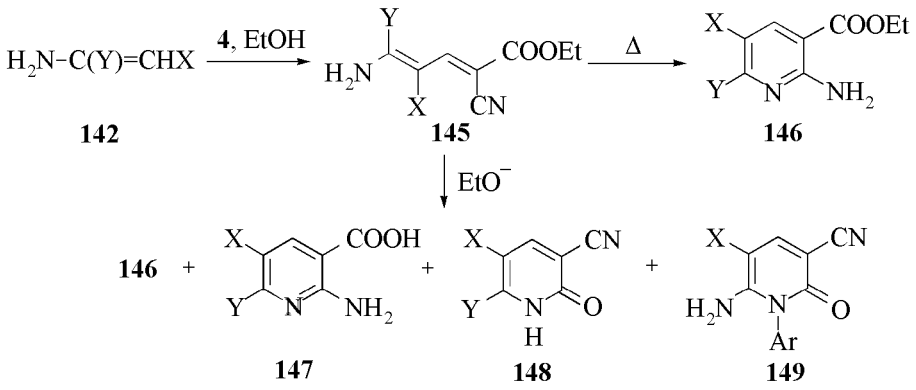
142 **143** **144**

X = CN, COOEt; Y = OEt, Het, AlkNH, ArNH.

At the use of linear enamines pyridines were obtained in very good yields. For instance, in reaction of enamines **142** with EMME in boiling ethanol were obtained in quantitative yield 2-(1*H*)-pyridones **144**. The latter at bioscreening showed strong inhibiting activity against *Blastomyces* and gram-positive microbes. These structures are likely to form via linear intermediate **143** that can be isolated from the reaction mixture when the process is carried out in an apolar solvent (CH_2Cl_2, benzene) and in the cold [71].

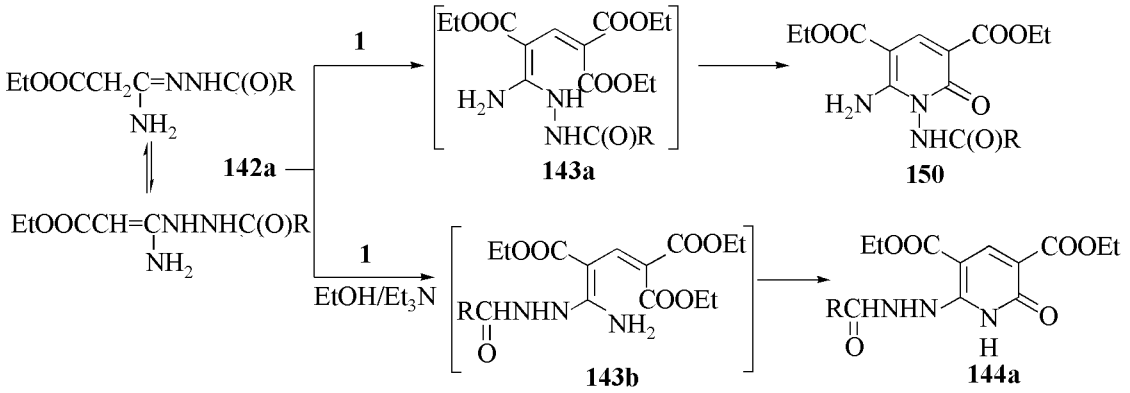
In the reaction of above enamines and similar compounds with unsymmetrical AOE, e.g., EMCA, the cyclization may occur both at ethoxycarbonyl and carbonitrile groups affording respectively 2(1*H*)-pyridones and 2-aminopyridines. For instance, the reaction of enamines **142** with EMCA in alcohol at room temperature gave rise to dienamine **145** whose ^{1}H NMR spectrum suggests *E*,*E*-configuration of the product. The thermal cyclization of alkene **145** afforded a single reaction product, derivative of ethyl 2-amino-3-pyridinecarboxylate **146**, whereas in the presence of sodium ethylate products of cyclization were obtained resulting from involvement into reaction both of ethoxycarbonyl group **148, 149** and of carbonitrile group **146, 147** [72].

EMME in DMSO/toluene on boiling with amidrazones **142a** in strait alcohol or in alcohol in the presence of acetic acid afforded in one stage 1-acylamino-2(1*H*)-pyridones **150**. The same reaction carried out in alcohol in the presence of triethylamine furnished 6-acylhydrazino-2(1*H*)-pyridones **144a**. The type of pyridone isomer is assumed to depend on the thermodynamical stability of intermediates **143a** and **143b** that are likely to form in the course of the



142 **145** **146** **147** **148** **149**

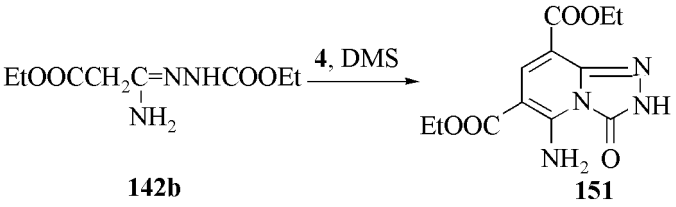
X = COOEt, CN; Y = OEt, NH_2, AlkNH, ArNH, Het.



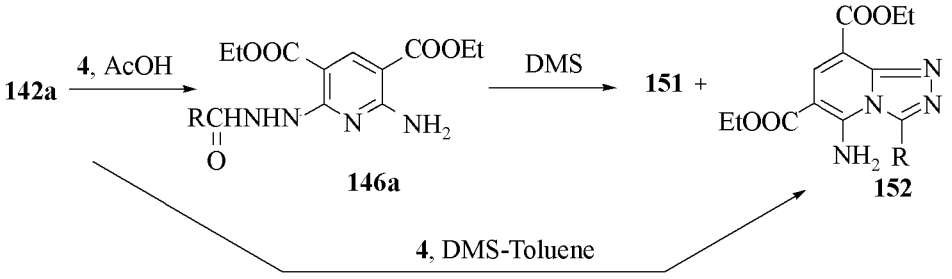
R = OEt, Alk, Ar, Het.

reaction. However the attempt to isolate the intermediates failed [73].

A study was performed of reaction between a structural analog of **142a**, compounds **142b**, and an ethoxymethylene derivative of the CH-acid containing two different groups capable of taking part in cyclization (EMCA). It was demonstrated that at boiling in DMSO or in DMSO toluene mixture the cyclization occurred at the cyano group giving 1,2,4-triazolo[4,3-*a*]pyridines **151**, and the reaction in AcOH at 20°C made possible isolation of intermediate products, 2-aminopyridines **146a** that on boiling in DMSO were converted into the corresponding triazoles **151** and **152** [74].

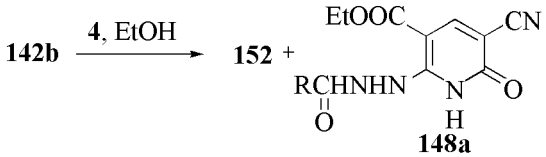


R = OEt, Alk, Ar, Het.



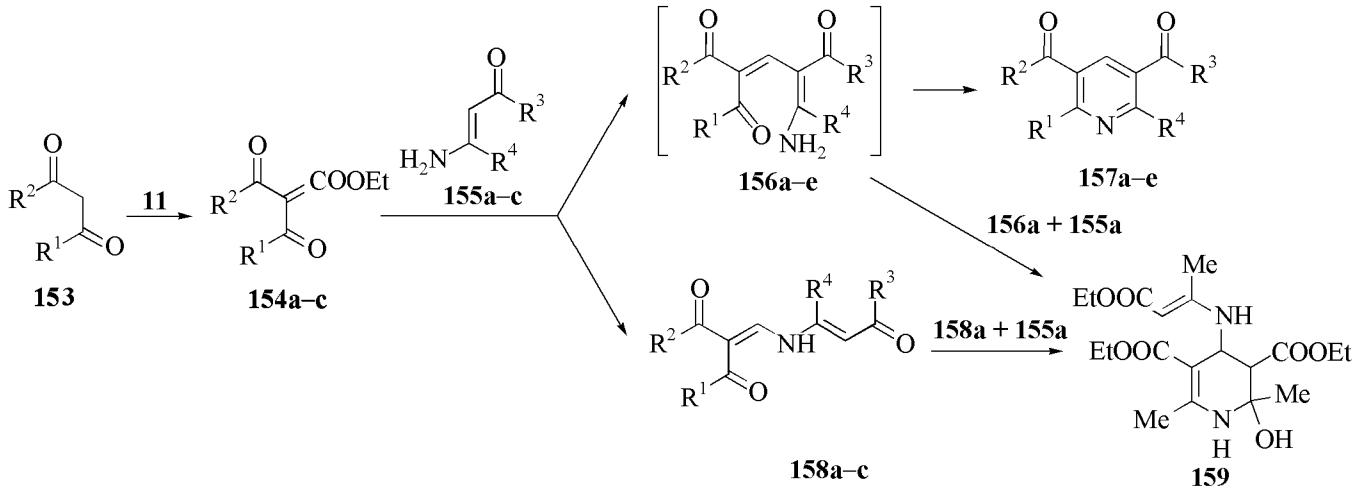
R = Alk, Ar, Het.

However when this reaction with compound **142b** was carried out in alcohol then apart triazole **152**, were obtained products of cyclization involving the ethoxycarbonyl group, 1,2-dihydropyridine-2-ones **148a** [74].

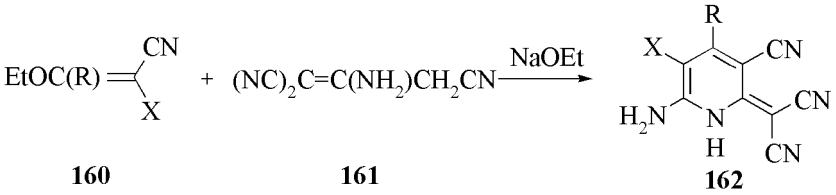


The condensation of β-dicarbonyl compound **153** and β-enaminocarbonyl compound **155** with TOF provided substances **157–159** whose formation occurred as follows. The reaction of β-dicarbonyl compounds **153** with triethyl orthoformate furnished their ethoxymethylene derivatives **154**. The latter react with enamines **155** both at the carbon nucleophilic site of these yielding dienamines **156** and at the nitrogen site providing dienamines **158**. Compounds **156** on cyclization afford pyridine structures **157**. The addition of aminoester **155a** to unsaturated diesters **156a** or **158a** followed by cyclization furnished tetrahydropyridine **159** [75].

Malononitrile dimer **161**, a CH-acid, on reaction with AOE **160** in alcoholic solution in the presence of



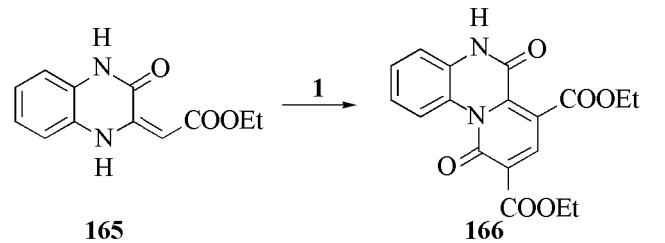
$R^1 = R^4 = Me$, $R^2 = R^3 = OEt$ (**a**); $R^1 + R^2 = R^3 + R^4 = CH_2CMe_2CH_2$ (**b**); $R^1 + R^2 = R^3 + R^4 = (CH_2)_3$ (**c**); $R^1 + R^2 = CH_2CMe_2CH_2$, $R^3 = OEt$, $R^4 = Me$ (**d**); $R^1 + R^2 = CH_2CMe_2CH_2$, $R^3 + R^4 = (CH_2)_3$ (**e**).

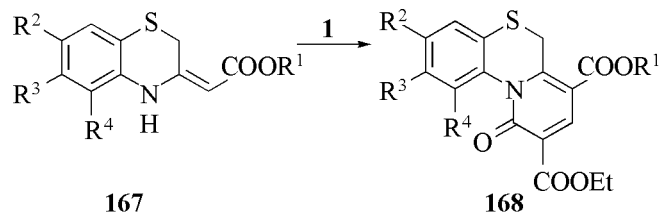


R = H, Me, Ph, Ar; X = CN, COOEt.

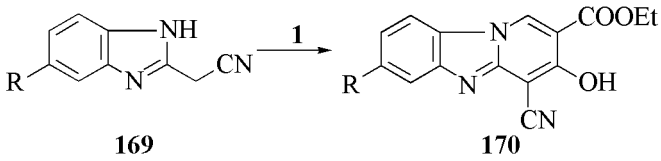
NaOEt followed by acidification with 35% HCl provides 1,2-dihydropyridines **162** [76].

The C–C–N fragment may be supplied by a compound containing this structure in a ring. In this case the compound possesses as a rule a methylene-active group taking part in S_NVin reaction with the ethoxy group of AOE or in cyclization of the S_NVin reaction product formed from a nitrogen atom and AOE. For





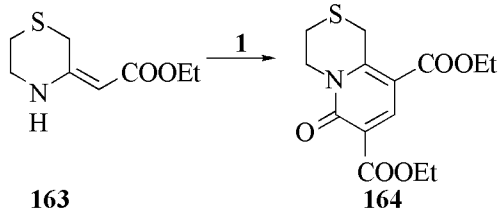
R^1 = Me, Et; R^2 = H, Cl, Me, OMe; R^3 = H, Me; R^4 = H, Cl.



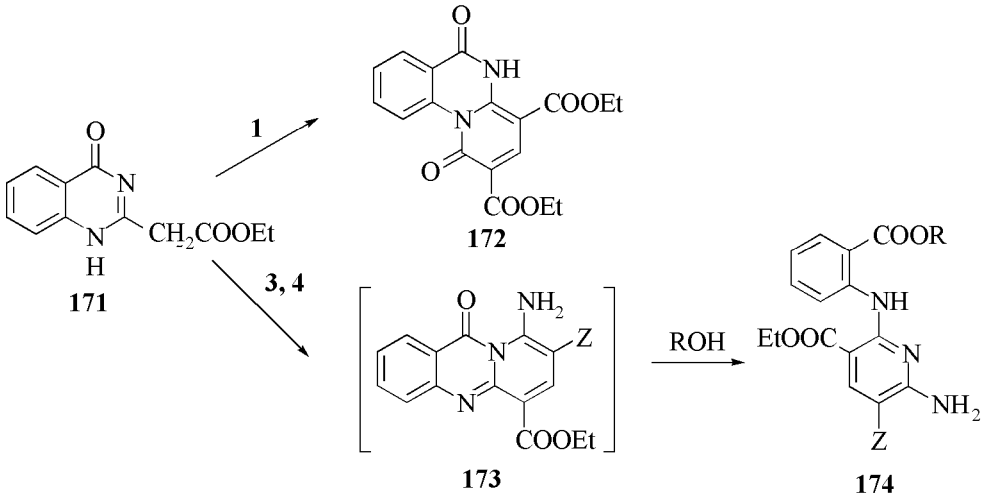
R = H, Me, Cl, OMe, NO_2

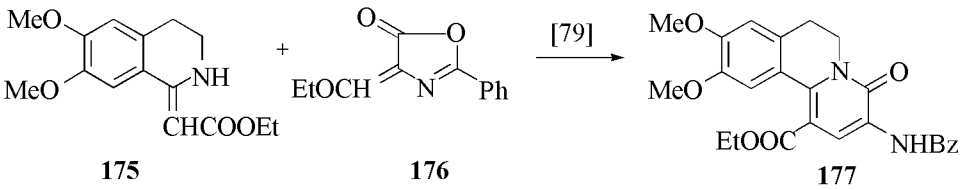
instance, reaction of ethers **163, 165, 167** with EMME furnishes respective fused pyridines **164, 166, 168** [77]. The derivatives of pyridines **164** and **168** are capable of binding benzodiazepine receptors.

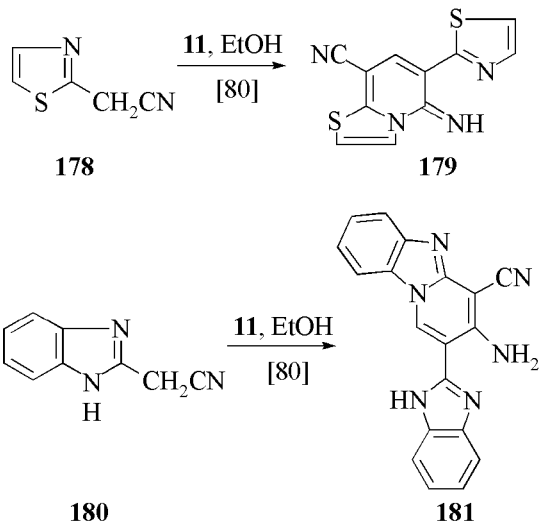
5-R-1*H*-Benzimidazol-2-acetonitriles **169** are condensed with EMME to give rise to ethyl 4-cyano-3-hydroxy-7-R-pyrido[1,2-a]benzimidazol-2-carboxylates **170** [78].



Reactions of quinazoline **171** with different derivatives of ethoxymethylenemalonic acid result in qualitatively unlike products. The reaction with EMME



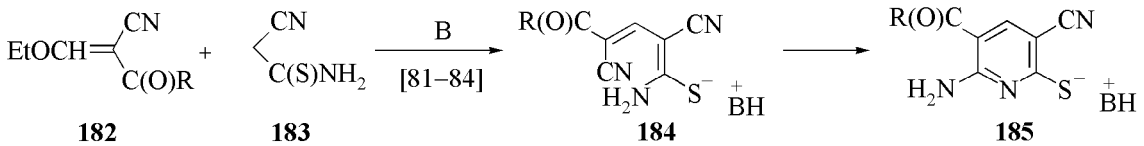


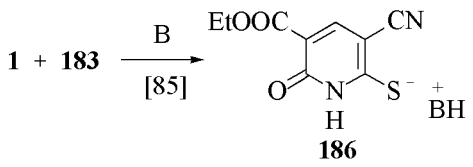


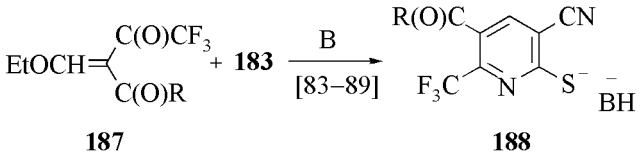
(without solvent at 180°C) afforded in good yields cyclization product at 1-nitrogen, pyrido[1,2-*a*]quinazoline **172**. With EMMN and EMCA in ethanol or ethanediol arise in good yield ethyl 2-(pyridin-2-yl)-aminobenzoates **174** which likely originate from solvolysis of tricyclic intermediate **173** [55].

In the reaction of ether **175** with AOE **176** fused pyridine **177** was obtained, and three-component condensation of nitriles **178** and **180** with TOF afforded fused pyridines **179** and **181** which apparently formed through ethoxymethylene intermediates.

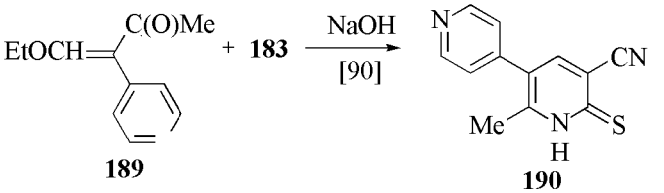
The reactions of AOE **1, 4, 182, 187, 189** with a fragment C–C–N from amides of substituted (thio)-acetic acid **183, 191, 193** afford 4-unsubstituted pyridines. This process occurs in the presence of a base giving products of S_NVin, which may be stable compounds that then can be isolated, as butadiene **184**. However they as a rule undergo cyclization

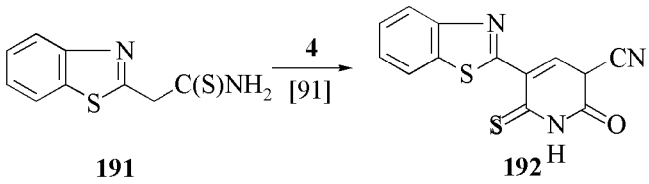


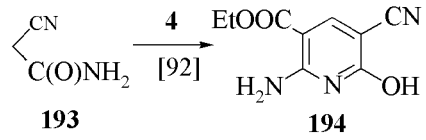


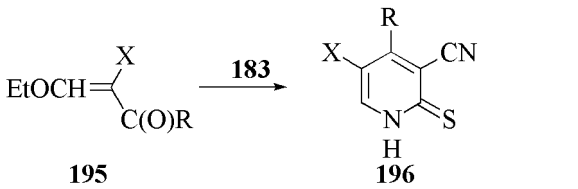


R = 2-thienyl, Ph; B = N-methylmorpholine.









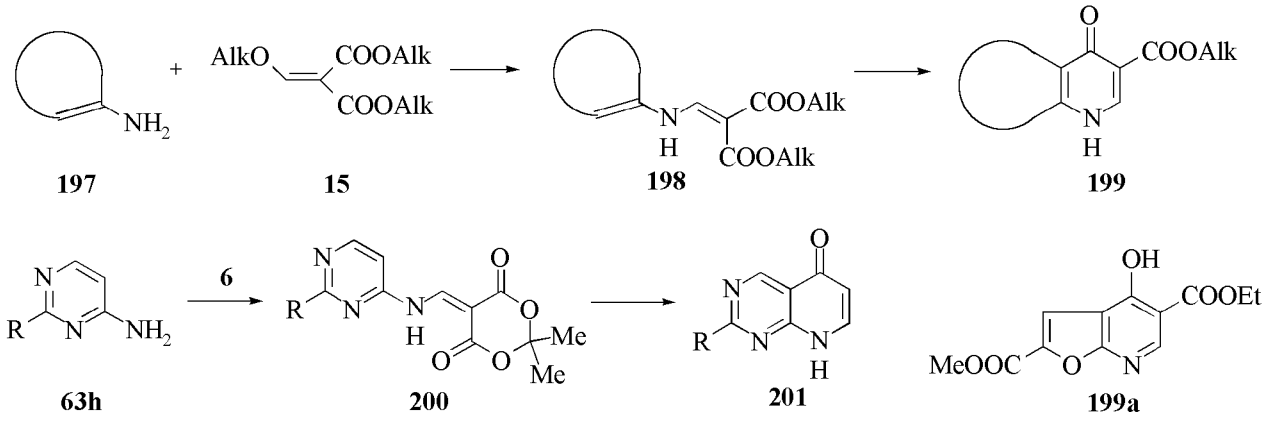
R = Me, Ph, $BzCH_2$; X = Ac, Bz, COOEt, CN

under the reaction conditions furnishing 4-unsubstituted pyridines **185, 186, 188, 190, 192, 194**.

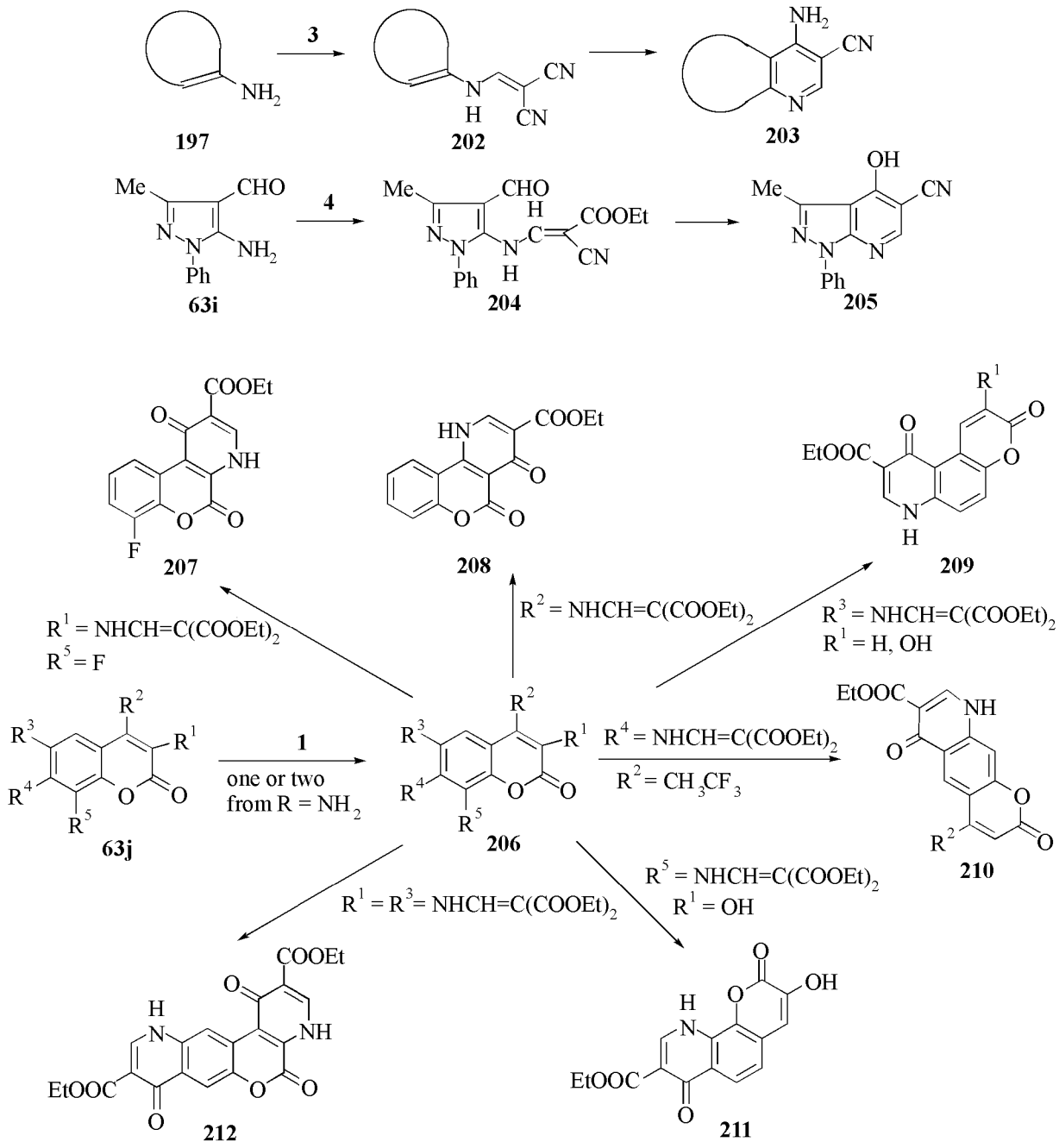
Preparation of 6-unsubstituted pyridine **196** along this reaction was reported in [93]. Taking into account the above considered processes this structure seems dubious. The compound obtained was likely 4-unsubstituted pyridine.

The syntheses utilizing the C–C–N fragment from aromatic amine **197** were named Gold–Jackobs reaction. Intermediates resulting from the S_NVin reaction **198, 200, 202, 204** are further subjected to cyclization under various conditions (boiling in Ph_2CH, *t*-BuPh, Ph_2O, in a mixture diphenyl ether–biphenyl; cyclization at heating in Dowtherm, treating with EtONa in an alcohol, with PPA) to furnish fused pyridines **199, 201, 203, 205**. The cyclization as a rule takes a single route at one of the two *ortho*-positions. The selectivity of attack effected by the carbonyl (carbonitrile) carbon depends here on several factors. The *ortho*-position of the ring does not take part in the cyclization if a substituent attached thereto is linked through a heteroatom (S, O) or if at the neighboring position occurs a bulky substituent. If one *ortho*-position contains a substituent, and the other one is a bivalent heteroatom (S), then cyclization occurs at the first *ortho*-position with elimination of the substituent.

Thus the reactions with ethyl alkoxymethylenemalonate afford fused 3-alkoxycarbonyl-4-oxo(oxy) **199** [94–106], with the Meldrum's acid methoxymethylene derivative fused 1,4-dihydropyridones-4 **201** [107], with EMMN fused 4-amino-3-cycnopyridines **203** [108–110], and with EMCA fused 4-hydroxy-3-cyanopyridines **205** [110].



R = Ar, Het.



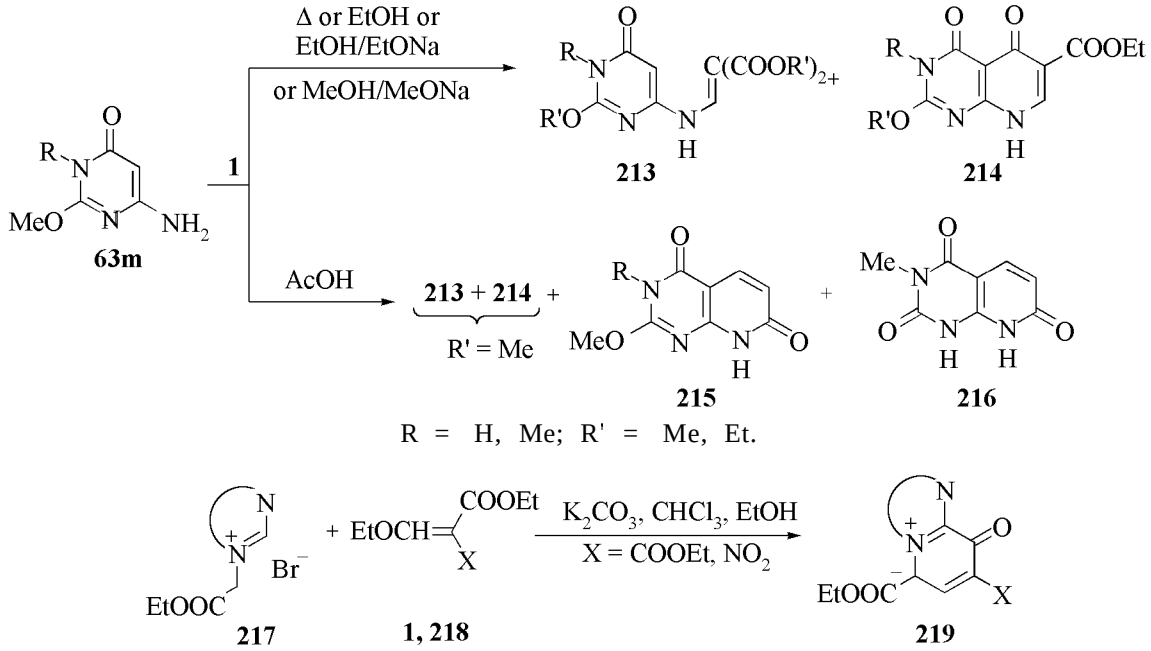
Pyridines **199** exhibit a wide range of biological activity: antimicrobial, malaricidal, anxiolytic, anticonvulsant, sedative, hypotonic effect, and pyridine **199a** have been used in the synthesis of the key intermediate of the inhibitor of HIV-protease, L-754394. Pyridines **203** possessed antimicrobial qualities.

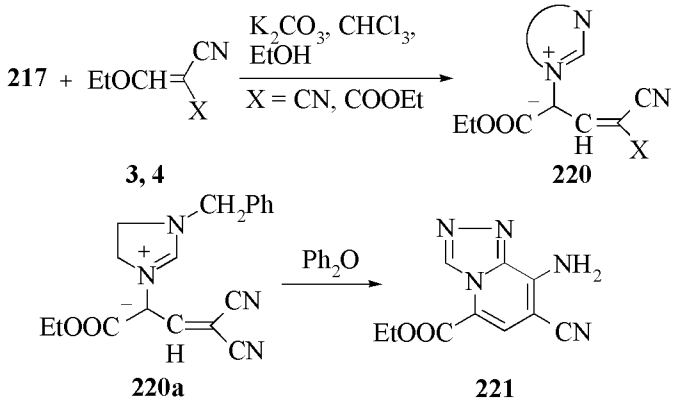
Preparation of various coumarin derivatives basing on Gold–Jackobs reaction was studied in detail. In the first stage of reaction mono- or diaminocoumarins **63j** were treated with EMME to get products of S_NVin **206**. On heating the latter in Dowtherm A the expected tricyclic esters **207**–**211** and tetracyclic diester **212** were obtained [111]. Ester **211** exhibited a high antimicrobial activity.

The investigation of reaction between 6-aminopyrimidin-4-ones **63k** with EMME in various media gave interesting results. It was shown that the reac-

tion carried out without solvent, in ethanol, in ethanol with sodium ethylate, or in methanol with sodium methylate followed a usual course and afforded products of *N*-alkylation **213** and **214**. Derivatives of aminomethylenemalonic acid **213** undergo cyclization into pyrimidopyridones **214** at heating in diphenyl oxide. When the reaction is performed in a boiling acetic acid it does not occur regioselectively and alongside **213** and **214** form also products of C-alkylation that further suffer decarboxylation: substances **215** and **216** [112].

The syntheses involving combination of fragments C–N–C and C–C–C are represented by reactions of triasole ylides (C–N–C fragment) with AOE (C–C–C fragment). Thus reaction of salts **217** with polarized olefins **1**, **218** in the presence of K_2CO_3 results in products of the so-called reversed 1,6-cyclization, mesomeric betaines **219**. In contrast the reaction with EMCA and EMMN is ended at the stage of N-allylides **220** formation, and the attempts to obtain the corresponding betaines were unsuccessful. It was however found that boiling of compound **220a** in the

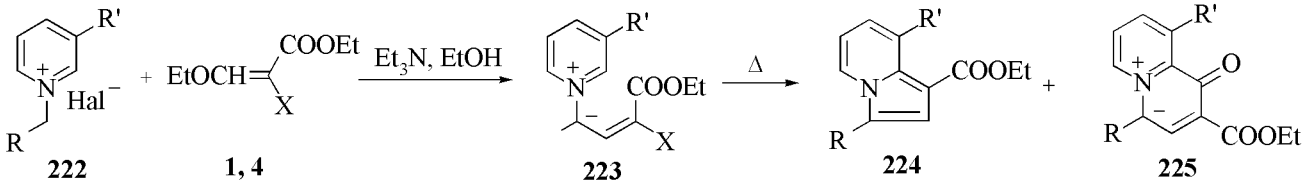




diphenyl ether afforded debenzylated product **221** [113–115].

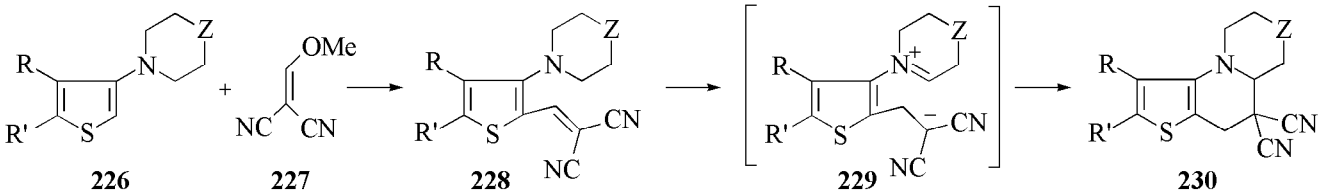
When a structure belongs to the pyridine series **222** the reaction with EMME or EMCA in alcohol in the presence of Et_3N leads to the corresponding products of S_NVin **223** which at boiling in xylene undergo cyclization providing a mixture of pyrrolo-[1,2-*a*]-pyridines **224** and quinolizinium imides **225** [116].

The reaction combining fragments C–N–C–C and C–C is a convenient synthetic path to thieno[3,2-*e*]-indolizines, thieno[2,3-*c*]quinolizine, and to their [1]benzothieno analogs **230**. Thiophenes **226** and **231** with methoxymethylenemalononitrile **227** furnish products of S_NVin **228** and **232**. Further attempts to effect cyclization of enaminonitrile **232** under various conditions failed whereas the boiling of ylidene-malononitriles **228** in butanol resulted in cyclization product **230**. This cyclization occurs via 1,5-hydride shift followed by intramolecular addition of carbanion to the double bond of imine in intermediate **229**. 3-(1-Pyrrolidinyl)-benzofuran **233** with olefin **227**



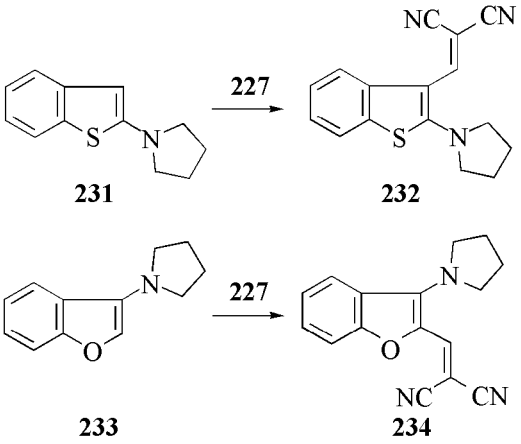
222 **1, 4** **223** **224** **225**

R = COOEt, CN, Bz; R' = NH_2, NHMe, NMe_2; X = COOEt, CN; Hal = Br, Cl.



226 **227** **228** **229** **230**

R, R' = H, Me, Ph; R + R' = CH=CH-CH=CH; Z = CH_2.



231 **232** **233** **234**

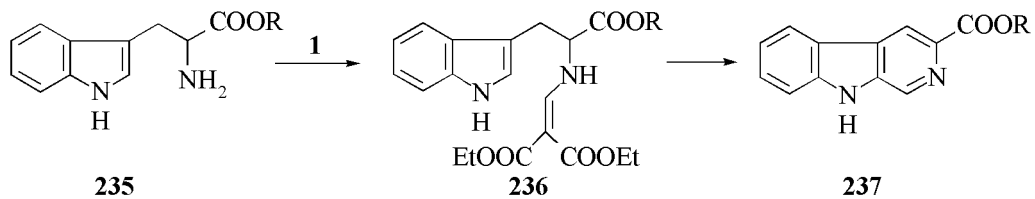
R = Me, Et.

furnished a similar substitution product **234** that failed to undergo cyclization [117].

It was already mentioned that under certain conditions the AOE may transfer a single carbon. This occurs in reaction of amino acid esters **235** with EMME in the presence of triethylamine. As a result arises product of S_NVin **236** which on treatment with TsOH in MeCN followed by work-up with Et_3N and AcOH in MeOH affords carbolin **237** [118].

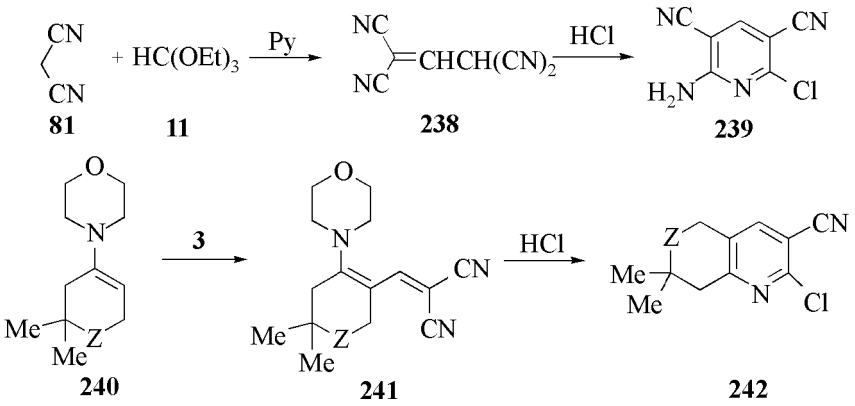
A cyano group can supply the nitrogen atom in the pyridine synthesis. For instance, in reaction of malononitrile with triethyl orthoformate or EMMN with heterocyclic system **240** formed respectively compounds **238** and **241**. Then the five-carbon chain obtained with a cyano group at C^1 on treating with hydrogen chloride in 2-propanol or acetic acid apparently was converted into imine or enamine which further underwent cyclization into 2-chloro-3-cyanopyridines **239** [119] and **242** [120].

Thus notwithstanding the versatility of synthetic approaches to the building up of a pyridine ring with the use of AOE certain general trends can be observed. The initial stage of reaction consists in S_NVin of alkoxy group by nitrogen or methylene-active fragment. In the first case always arise α-unsubstituted pyridines, in the second process depending on the position of the methylene-active fragment 3- or 4-unsubstituted pyridines are obtained. When alkoxyalkylidene(arylidene)CH-acids are used as AOE to the positions *3* and *4* will be attached the corresponding (alkyl or aryl) substituent.



235 **236** **237**

R = Me, Et.



Z = O, NMe.

II.3. *Quinolines*[*]

The methods of quinolines syntheses were isolated in a special section instead of mentioning them with those of pyridines because of enormous number of recent publications treating their preparation with the use of AOE. Besides the common target of obtaining biologically active substances is inherent to these publications. Therefore unlike the syntheses of the other heterocyclic systems discussed in this review a great number of quinolines preparation processes are protected by patents. Many among them found industrial application. The substituted quinolines, in particular, ethyl quinolin-4-one-3-carboxylates prepared by this procedure, either are semiproducts in the synthesis of biologically active substances, or possess themselves a versatile biological activity. The research carried out with these compounds showed their anti-HIV-RTA activity, activity against gram-positive and gram-negative, anaerobic and mycobacteria, against the pathogenic microflora of a number of veterinary infections. They also exhibited malaricidal and antitumor activity, acted as inhibitors of gastric (H^+/K^+)-ATP-ase, thyrokinase of protein *p* 56^{lck}, and topoisomerase of mammals, and were applied as radiosensitizers of hypoxic cells.

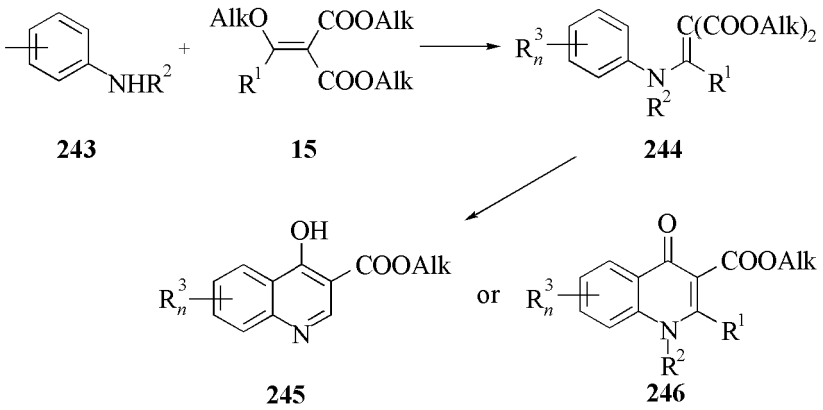
The quinolines under consideration are also applied to pharmacokinetic and pharmacodynamic research, they are used as anticonvulsant and sedative drugs, as hypoxy-selective anticancer medicines, antimicrobial drugs of reduced phototoxic effect, bactericides for urinary tracts. The physiologically admissible quinoline derivatives are used in pharmaceuticals (as pellets, dragee, capsules, pills, granules, suppositories, solutions, suspensions, emulsions, pastes, ointments, gels, creams, lotions, powders) for medicine and veterinary, and also as forage additives [122–243].

The main synthetic methods for quinolines involving AOE are Gold–Jackobs reaction and treating with amines of ethoxymethylene derivatives of halosubstituted aromatic acids containing a methylene-active fragment.

The Gold Jackobs reaction is effected by treating with aromatic amines **243, 125** AOE **4, 5, 15, 195a** to yield products of S_NVin **244, 247, 249, 251** which as a rule after isolation are submitted to cyclization into substituted quinolines **245, 246, 248, 248a, 252**. The cyclization conditions are quite different: Heating in Dowtherm A, in Ph_2O, chloroform, dodecane, in Ac_2O + H_2SO_4, treating with PPA at various temperature or under microwave irradiation. The most popular procedure for semiproduct condensation (heating in diphenyl oxide) has on industrial scale a number of drawbacks. The main shortcomings consist in relatively low yields (usually no more than 70%) and insufficient purity of the target product, formation of side products as aryl ketones, toxicity of Ph_2O, requirements for continuous Ph_2O recovery. It was found that the quinolines synthesis can be performed in one stage if the reaction is carried out in paraffin hydrocarbons C_{12}–C_{18} at condensation temperature 210–250°C. As a result the yield of quinolines increased up to 84% and their purity attained 96%. Thus instead of expensive Ph_2O it is possible to apply cheaper paraffin hydrocarbons that on separation of the target product can be many times used without additional purification [128].

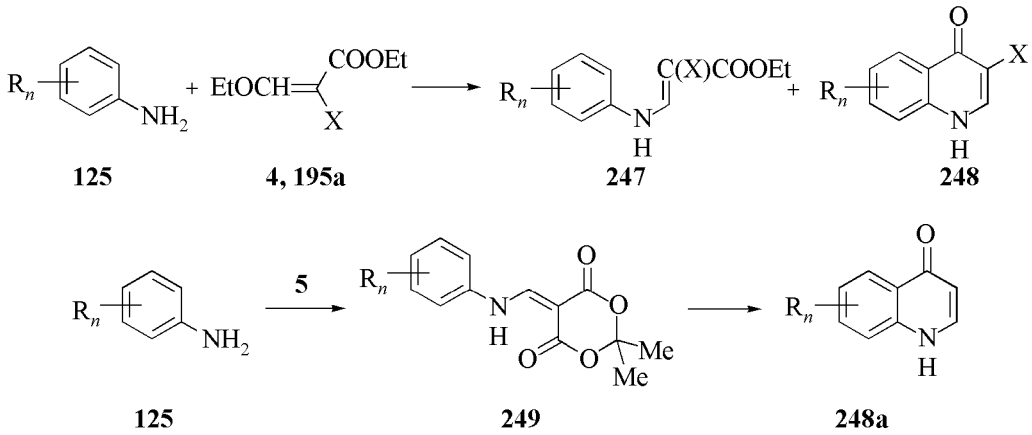
The ring closure occurs by electrophilic attack of the carbonyl group on the unsubstituted *ortho*-posi-

[*] Quinolines preparation methods described further are also valid for the synthesis of their analogs, naphthiridines. In this case instead of benzene ring is used that of pyridine. All data on the synthesis of these compounds including those with the use of AOE are comprehensively described in review [121].



243 **15** **244** **245** **246**

R^1 = H, Alk C^1–C^4, Ar, ArAlk; R^2 = Alk C^1–C^6, cycloalkyl, $CH{=}CH_2$, $PhCH_2$, Ac, $ArCH_2$, alkenyl; R^3 = H, Alk, Ar, Hal, OAlk, NHAlk; *n* = 1–4.



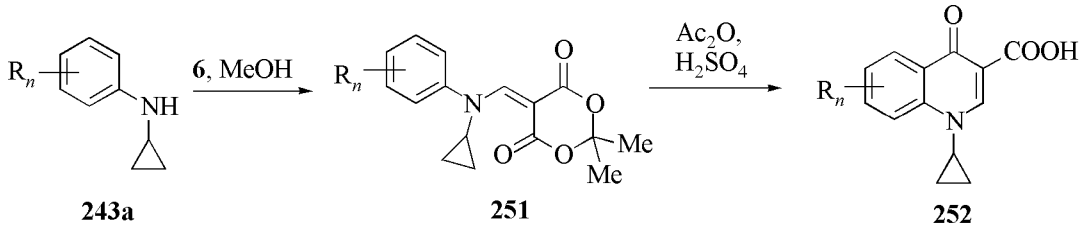
125 **4, 195a** **247** **248** **125** **249** **248a**

X = CN, COAlk; R = H, Alk, Ar, Hal, OAlk, NHAlk; *n* = 1–4.

tion with respect to amino group, and at the use of alkoxymethylene derivatives of malonic acid **15** affords 4-hydroxy(oxo)-3-alkoxycarbonylquinolines **245, 246** [122–169, 177, 179], and with other CH-acids **4, 195a** and **5** yields the corresponding 4-oxo-3-R-quinolines **248** [162, 163, 170–176] and **248a** [172, 177, 178].

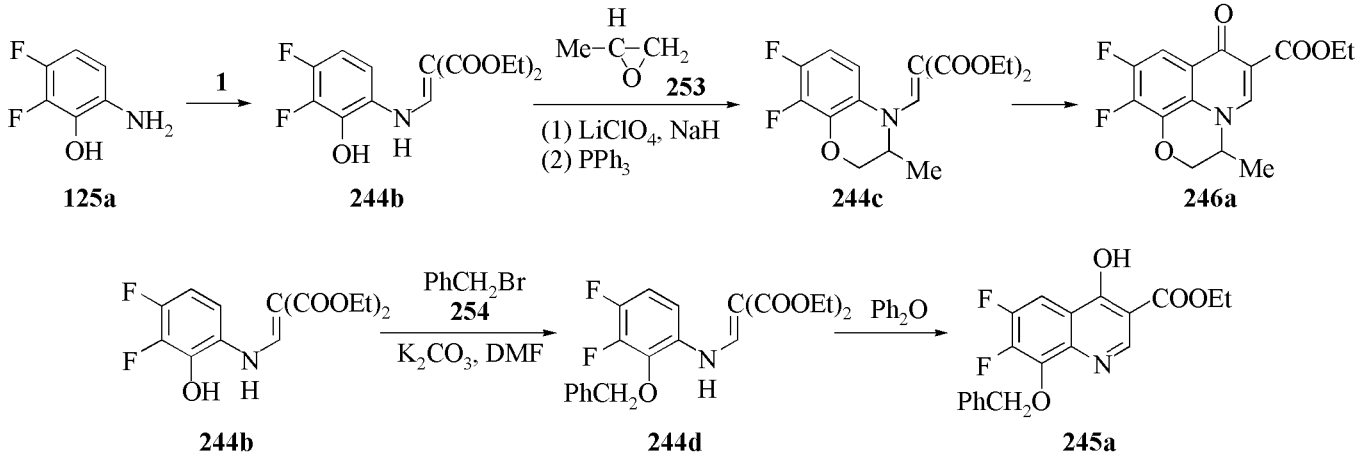
It should be noted that in all published descriptions of this reaction the cyclization always occurred just with participation of the ethoxycarbonyl group affording 4-oxy(oxo)quinolines. Even at the use of AOE lacking an ethoxycarbonyl group (EMMN etc.) the reaction ended at the stage of the product formed by S_NVin, and no data of further cyclization were reported.

When $POCl_3$ was used as cyclization agent in this reaction the resulting product was ethyl 4-chloroquinoline-3-carboxylate **250** [180].



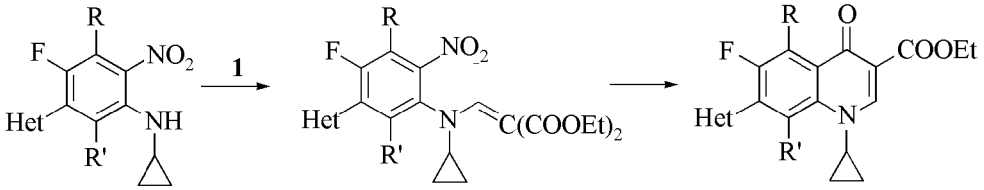
243a **251** **252**

R = H, Alk, Ar, Hal; *n* = 1–4.



Reaction with ethoxyolefin **6** commonly yields 3-unsubstituted quinolines **248a**. However the process carried out in acetic anhydride in the presence of sulfuric acid affords quinoline-3-carboxylic acids **252** [179].

The arising intermediate also can be modified before cyclization. For instance, boiling of 2-hydroxy-3,4-difluoroaniline **125a** with EMME in ethanol gave the product of S_NVin **244b** whose reaction with racemic propylene oxide **253** in the presence of $LiClO_4$ and NaH followed by treating the reaction product with PPh_3 and diethyl azodicarboxylate in ethyl acetate resulted in [1,4]benzoxazine **244c**. The latter further was subjected to cyclization to obtain compound **246a** that then was converted in an antibiotic of versatile activity, ophloxancin. Similarly is prepared the S-isomer of the latter, levophloxacin, applying to the synthesis the R-propylene oxide [181].



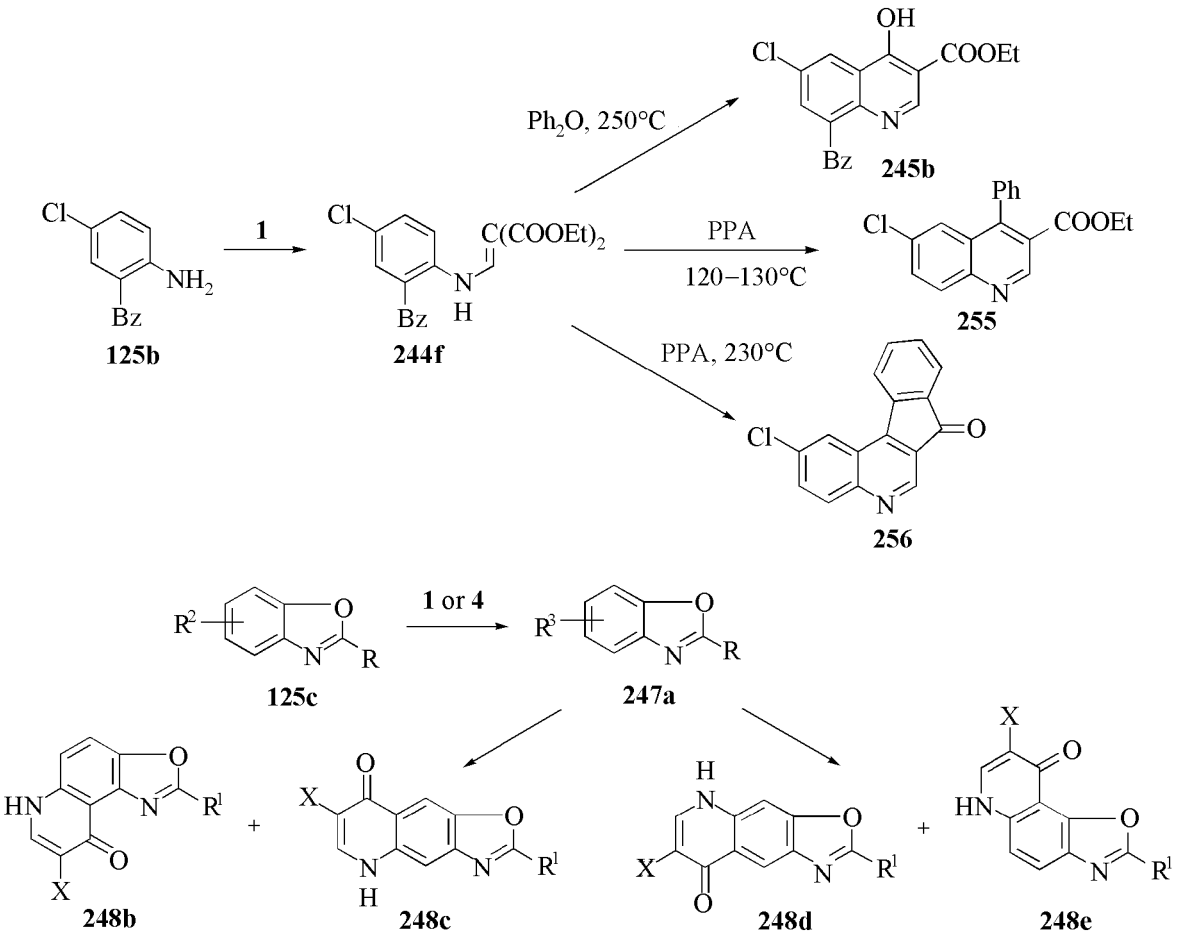
R = H, Me; R' = H, Me.

N-substituted aminomethylenemalonic ester **244b** can react with benzyl bromide **254** affording O-alkylated derivative **244d**. The latter undergoes cyclization by common procedure yielding quinoline **245a** [182].

The cyclization of **244** intermediate in most cases provides a product of carbonyl attack on one of the two *ortho*-positions which is chosen by the following reasons: the cyclization occurs at the *ortho*-position without substituents, and in case both *ortho*-positions are unsubstituted then the attack takes place exclusively at the least sterically hindered site (with no bulky groups in the vicinity).

However this rule holds always only under the conditions stated above, and on changing the cyclization procedure a substitution of a group attached to one of the *ortho*-positions may occur. At the same time the second *ortho*-site, be it substituted or not, does not take part in the reaction. For instance, the reaction of substituted nitroaniline **243b** with EMME gave rise to semiproduct **244e** that on cyclization in the acetic anhydride in the presence of H_2SO_4 afforded a product of nitro group substitution, quinoline **246b** [183, 184].

The cyclization can proceed similarly when to one of the *ortho*-positions is linked a reactive group, and the reaction conditions are suitable. For instance, the cyclization of amine **244f** by heating in Ph_2O at 250°C furnished ethyl 4-hydroxyquinoline-3-carboxylate **245b**. The cyclization of compound **244f** by



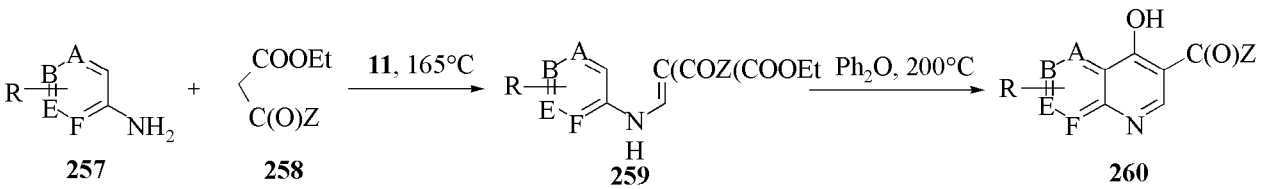
X = COOEt, CN; R^1 = H, Me, Ph; R^2 = 5- or 6-NH_2; R^3 = 5- or 6-NHCH=C(X)COOEt.

treating with PPA at 120–130°C or 230°C afforded respectively ethyl 4-phenylquinoline-3-carboxylate **255** and 7*H*-indeno[2,1-*c*]quinolin-7-one **256**. The latter resulted from cyclization with participation of a benzoyl group [185].

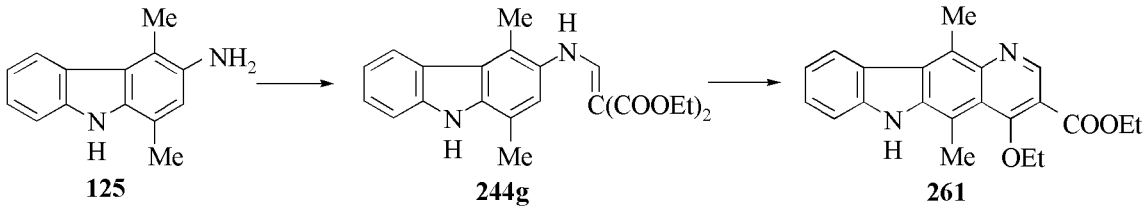
The cyclization in the case of both equal *ortho*-positions occurs at both sites. Thus the condensation of 5-and 6-amino-2-R-benzoxazoles **125c** with AOE **1, 4** gave rise to products of S_NVin **247a**, which on heating underwent cyclization affording a mixture of angularly and linearly fused oxazoloquinolines **248b**–**248e** [186, 187].

A modified version of this procedure was developed in [188]. Quinolines and various aza derivatives thereof **260** are prepared in a three-component reaction of amine **257**, TOF, and CH-acid **258** subjecting the intermediate **259** obtained to subsequent cyclization.

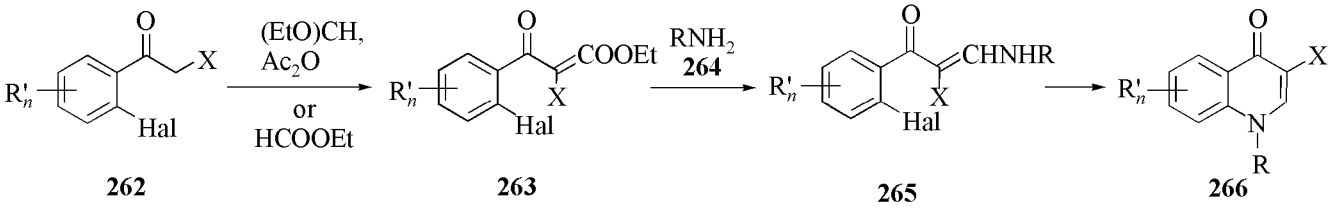
The cyclocondensation of intermediate of **259** type almost always occurs with alcohol liberation, but at their sublimation another path is possible involving water elimination. Thus in reaction of 9*H*-carbazole **125d** with EMME product of S_NVin **244g** was obtained that on sublimation at 200°C afforded pyridocarbazole **261** [189].



Z = Ph, Ar, Het; R = H, Hal, OMe; A = C = E = F = CH or one of them = N.



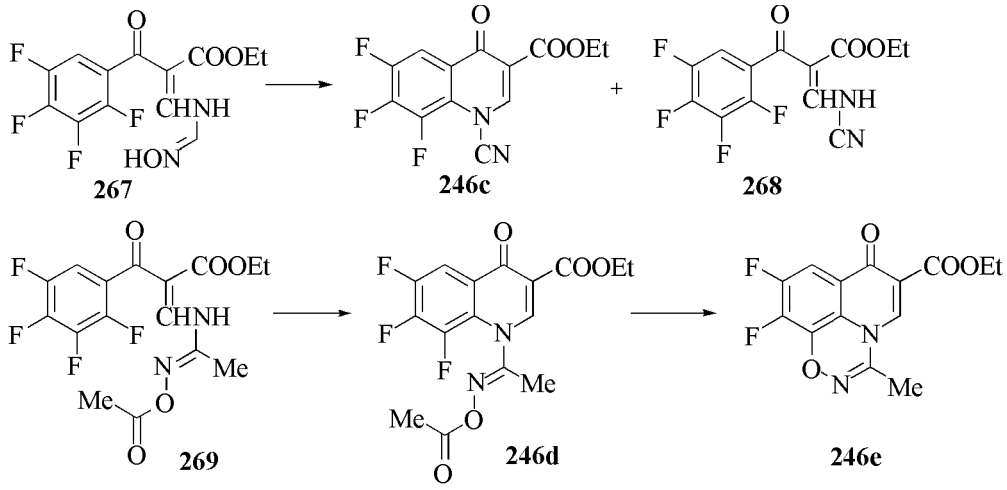
As initial reagents for the second method of quinolines synthesis involving AOE serve halogen-substituted aromatic systems possessing methylene-active fragment **262**. The latter is reacted with a mixture of triethyl formate and acetic anhydride or with ethyl formate to furnish its ethoxymethylene derivative **263** which after separation or without it reacts with amine **264**. The cyclization of arising product of S_NVin **265** was usually effected by various bases in aprotic solvents: by NaH in dioxane, THF, *N*-methyl-2-pyrrolidone, in anhydrous ether, glyme, monoglyme, hexane, DMF, DME; by K_2CO_3 or Na_2CO_3 in MeCN, xylene, DMF, acetone; by boiling with K_2CO_3 and 18-crown-6 in MeCN; by Et_3N; by *t*-BuOK in *t*-BuOH or THF; by KF or NaF in DMF or MeCN; by NBu_4F in THF; the cyclization was performed in THF in N_2 atmosphere, or by boiling in toluene. In this reaction a regioselective halogen substitution was observed of the halogen atom in the *ortho*-position to the given substituent resulting in formation of ethyl 4-quinoline-3-carboxylate **266** [190–240].

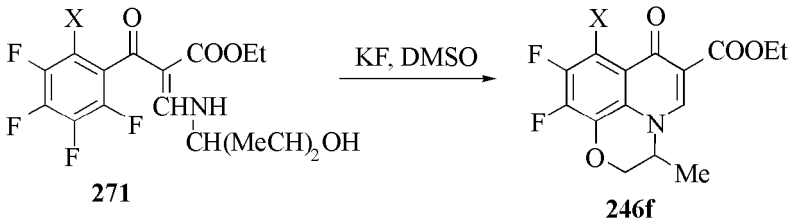


X = COOAlk, COCOOEt; R = Alk, cycloalkyl, vinyl, haloalkyl, hydroxyalkyl, Ar, naphthyl-1, naphthyl-2, Het, CH=NOH, $(CH_2)_3NMe_2$, $CH(Me)CH_2SPh$, $(CH_2)_2OPh$, oxetan-3-yl; R' = H, Alk, Ar, Het, Hal; *n* = 1–4.

The amine involved into the reaction may contain a substituent capable of modification at the cyclization stage. For instance, ester **267** treated with the cyclization agent afforded a mixture of cyclic and open-chain esters **246c** and **268**, and ester **269** furnished a mixture of quinoline **246d** and tricycle **246e** [241].

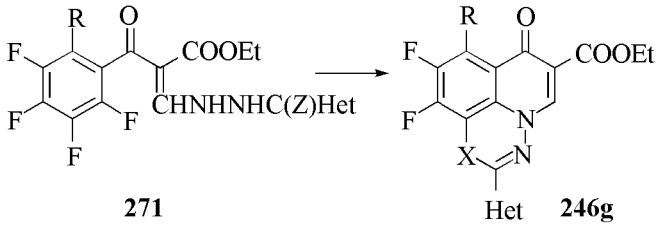
Ester **270** treated with KF in DMSO underwent cyclization into tricycle **246f** [242], and ester **271** on





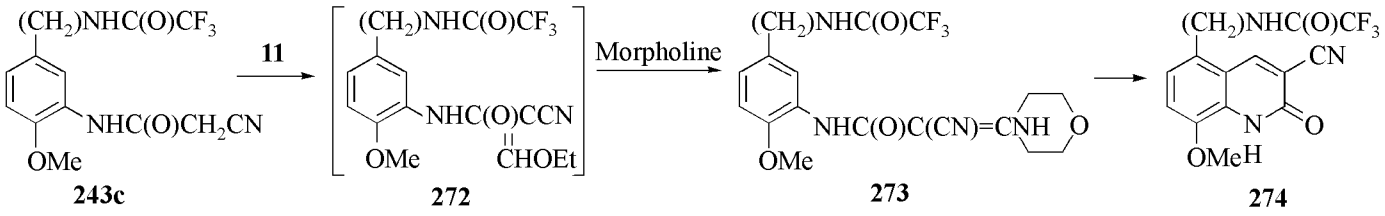
271 **246f**

X = F, MeS, PhCH2NH, NH2, PhCH2O, OH.



271 **246g**

R = H, F; Z = O, S.



243c **272** **273** **274**

boiling in toluene or in MeCN with KF was converted into tricycle **246g** [243].

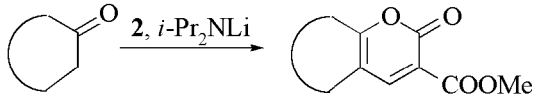
In [244] a reaction was described differing from the two methods discussed above: The reaction of CH-acid **243c** with triethyl formate and morpholine through AOE **272** stage led to enamine **273** which on cyclization and deprotection afforded 1(*H*)-quinolin-2-one **274**.

Thus one of the principal methods of preparation for quinoline derivatives which in the last decades attracted great interest due to their versatile biological activity consists in S_NVin of an ethoxy group by a nitrogen atom in the course of one stage of the synthesis. Some compounds of this class are already prepared by this procedure on an industrial scale, and optimum conditions of the reaction are developed.

II.4. *Pyrans*

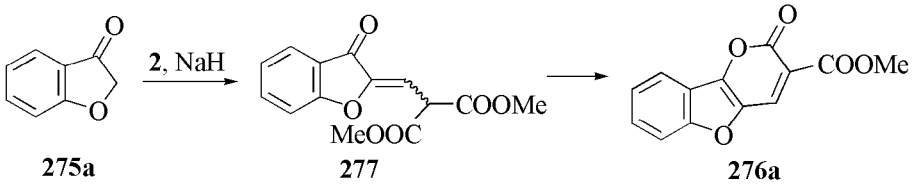
α-Pyrones are synthesized using AOE by S_NVin A reaction with some methylene-active reagent which in this case is a cyclic ketone, an open-chain or cyclic dicarbonyl compound, thiobarbituric acid derivative, or pyridinium ylide. In reaction with AOE the latter compounds form products of S_NVin that on cyclization give the corresponding α-pyrones.

By reaction of cyclic ketones **275** with methyl methoxymethylenemalonate in the presence of *i*-Pr_2NLi α-pyrones **276** were obtained originating from reaction of ketone methyl group with the olefin followed by cyclization [245, 246].



275 **276**

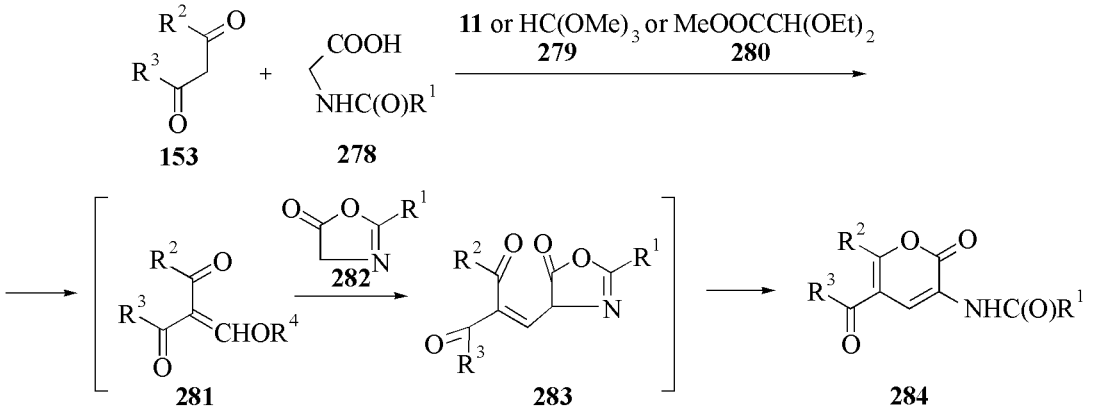
By reaction of 3-oxo-2,3-dihydrobenzofuran **275a** with compound **2** in THF in the presence of NaH 2-ethylidene-3-oxo-2,3-dihydrobenzofurans **277** were obtained as a mixture of *E*- and *Z*-isomers. The latter on boilig in xylene underwent cyclization into fused α-pyrones **276a** [247]. A simple one-pot synthesis of 2*H*-pyran-2-ones and fused pyran-2-ones **284** consists in reaction of 1,3-dicarbonyl compound **153**, TOF or $CH(OMe)_3$ **279** or diethoxymethyl acetate **280** transfering one carbon atom, N-substituted glycine **278**, and a large excess of acetic anhydride, likely with participation of structures **281**–**283**. Although from unsymmetrical 1,3-dicarbonyl compounds two types



275a **277** **276a**

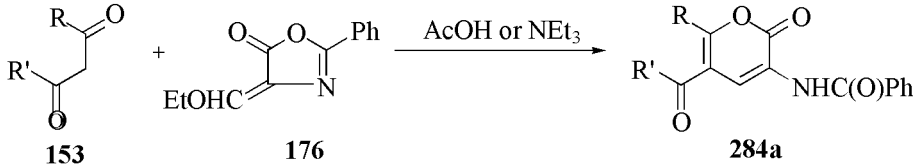
of pyranones could have formed, a single cyclization product was obtained originating from reaction at the carbonyl carbon in position *4* with respect to heteroatom [248, 249].

Similar products were obtained by reaction of 4-ethoxymethylene-2-phenyl-5(4H)oxazole **176** with the corresponding methylene-active compounds **153** [250].



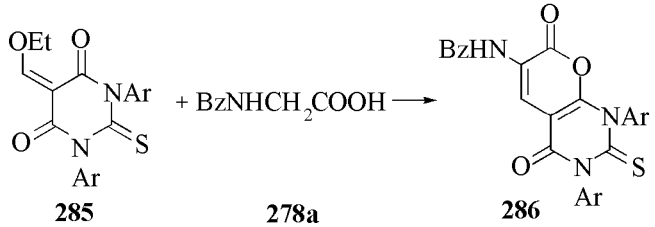
153 **278** **281** **283** **284**

R^1 = Me, Ph, 2-pyrazinyl, 3-pyridinyl; R^2 = Me; R^3 = Me, OEt; R^2 + R^3 = cycloalkenyl, heterenyl; R^4 = Me, Et.



153 **176** **284a**

R = CH2COOMe; R' = OMe; R + R' = cycloalkenyl, heterenyl.

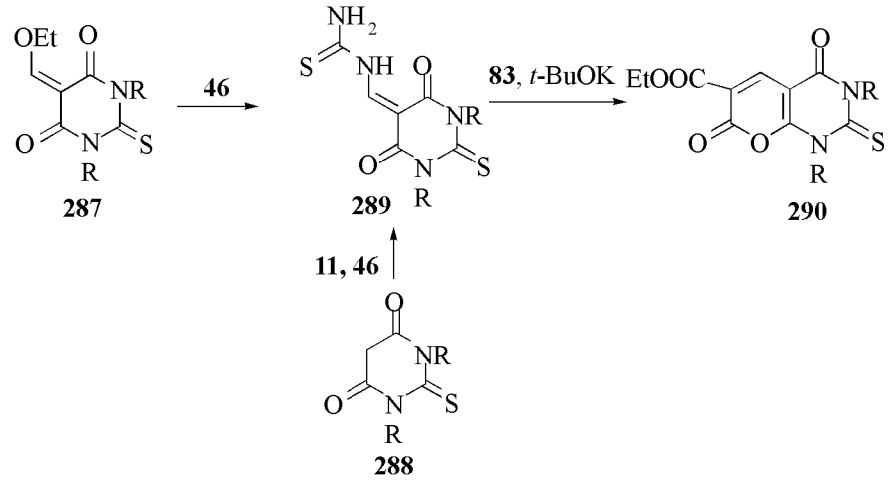


285 **278a** **286**

The preparation of fused pyrans from derivatives of 1,3-di(R-phenyl)-2-thiobarbituric acids **288** and various AOE obtained both from thiobarbituric acid and the other CH-acids was studied in [251]. For instance reaction of AOE **285** with amino acid **278a** in acetic anhydride after cyclocondensation afforded in 92% yield derivatives of 1,2,3,4-tetrahydro-7*H*-pyrano[2,3-d]pyrimidin-7-one **286**.

By reaction of olefin **287** with thiourea or by three-component condensation of thiobarbituric acid derivative **288**, TOF, and thiourea 5-ureidomethylene-1,3-di-R-2-thiobarbituric acids **289** were obtained which on treatment with ethyl cyanoacetate in the presence of *t*-BuOK undergo cyclization affording in 62–68% yield 1,2,3,4-tetrahydro-2-thioxo-4-oxo-7*H*-pyrano[2,3-d]pyrimidin-7-ones **290** [252].

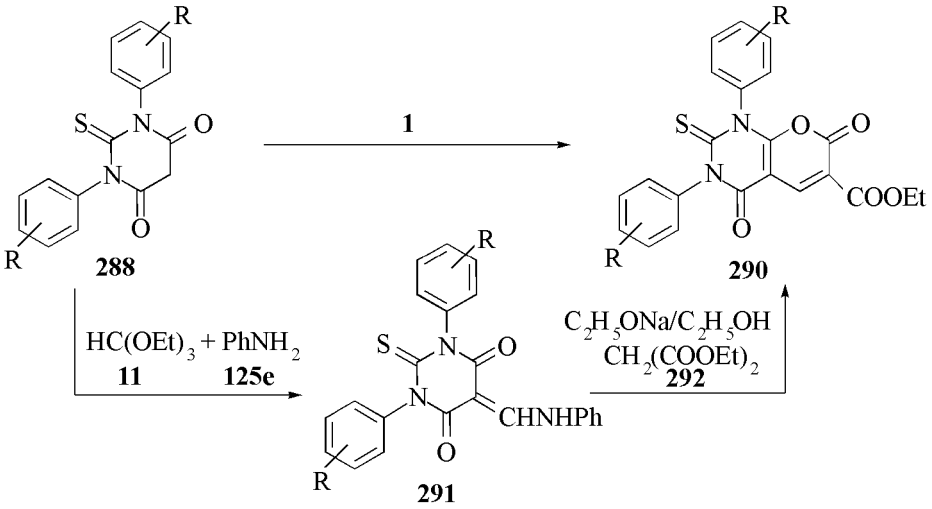
The condensation of thiobarbituric acid derivative **288** with EMME in acetic acid provided in one stage 7*H*-pyrano[2,3-d]pyrimidines **290**. The alternative



287 289 290 288

R = Ph, Ar.

synthesis of this compounds consists in reaction of compound **288** with TOF and aniline **125f** followed by treating the obtained derivative of 5-aminomethylene-2-thiobarbituric acid **291** with diethyl malonate **292** in the presence of sodium ethylate in alcohol [253].

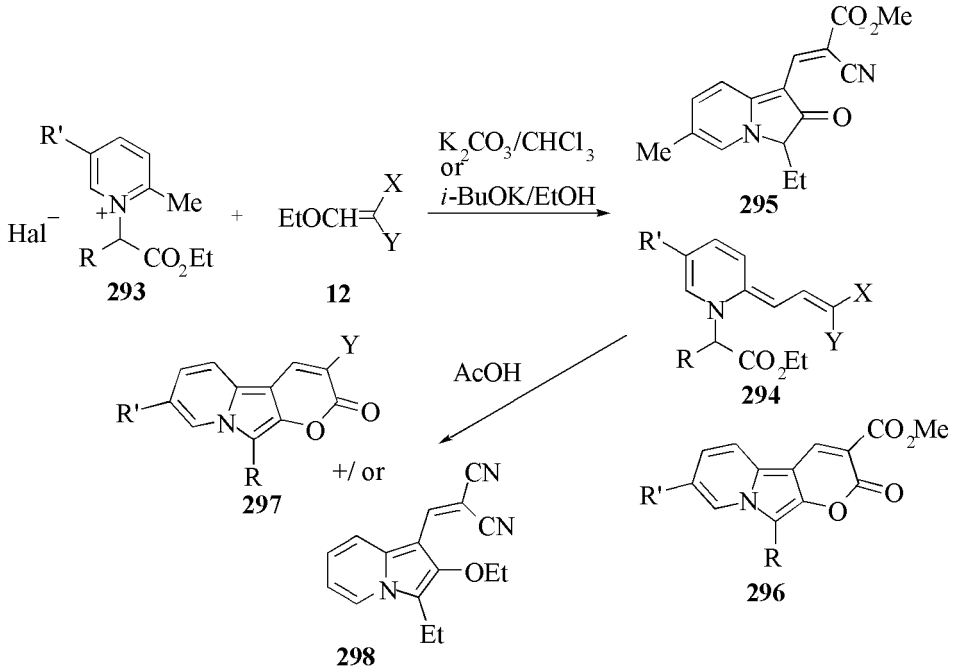


288 290 291

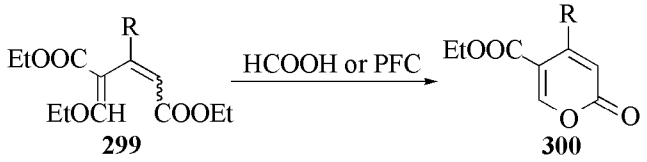
R = H, 2-OMe, 3-OMe, 2-Me, 3-Me, 4-Me, 4-Cl.

The reaction of ylides **293** with AOE **12** in the presence of a base gave rise to derivatives of 1,2-dihydropyridine **294**; therewith in the case of 1-(1-ethoxycarbonylpropyl)-2,5-dimethylpyridinium bromide and methyl 2-ethoxymethylene-2-cyanoacetate formed also derivative of 1-vinylindolizin-2-(3*H*)-one **295** in 70% yield, and at the use of ethyl ethoxymethyleneacetoacetate in the presence *t*-BuOK in ethanol alongside dienes **294** form in a low yield (3–6%) also derivatives of 2*H*-pyrano[3,2-a]indolizin-2-one **296**. Dienes **294** on boiling in acetic acid afford in 12–45% yield the corresponding derivatives of 2*H*-pyrano[3,2-a]-indolizin-2-one **297**. Ethyl ether of 2-(3,3-dicyanoallylidene)-1-(ethoxycarbonylpropyl)-1,2-dihydropyridine under conditions of this reaction also afforded 2,2-dicyanovinyl-2-ethoxy-3-ethylindolizine **298** [254].

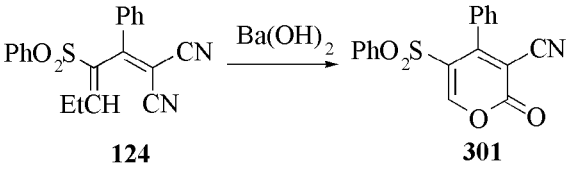
α-Pyrones may be also obtained by treating an existing C_5-chain with cyclization reagents. For instance, AOE **299** in the presence of formic or polyphosphoric acid or AOE **124** in the presence of barium hydroxide furnished respectively α-pyrones **300** [255] and 301 [66].



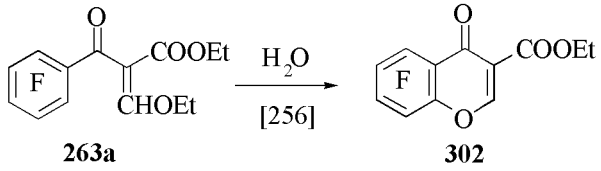
Hal = Cl, Br; R = H, Me, Et; R^1 = H, Me, Et; X = CN, COMe; Y = CN, COOMe, COOEt.

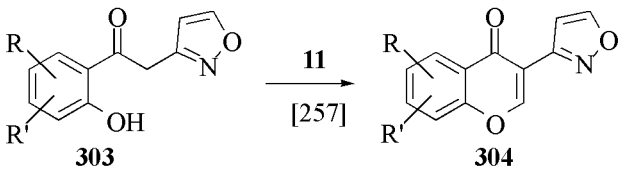


R = H, F, Cl, EtO, $PhCH_2S$, CH_3SO_2, Bu, COOEt, Ph.

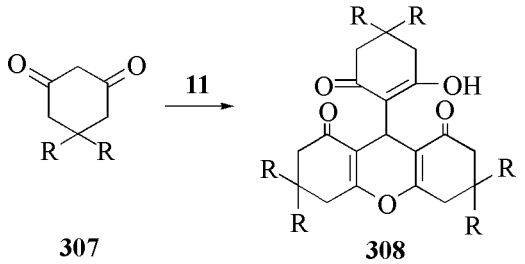


Chromones **302, 304, 306** are prepared from ethoxymethylene derivatives of various CH-acid containing a benzoyl group as an electron-acceptor substituent. Therewith the cyclization mechanism and consequently the structure of reaction products depend here on the structure of the second electron-acceptor group. When the latter is ethoxy group (compound **263a**) or isoxazolyl-3-carbonyl moiety (compound **303**) then nucleophilic substitution of fluorine or hydroxy group in the aromatic ring is observed to afford respectively chromones **302** and **304**. At the use of ethoxymethylene derivative of ethyl pentafluorobenzoylpyruvate **263b** the expected 3-ethoxyallylchromone failed to form for the latter



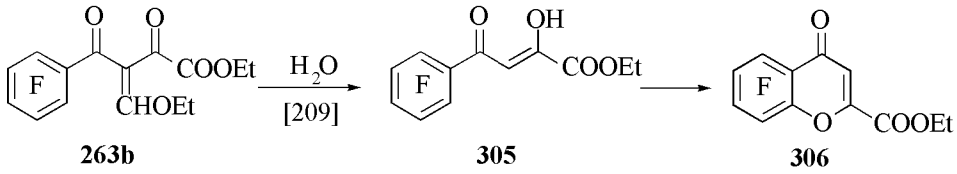


R, R' = H, Alk, OH.



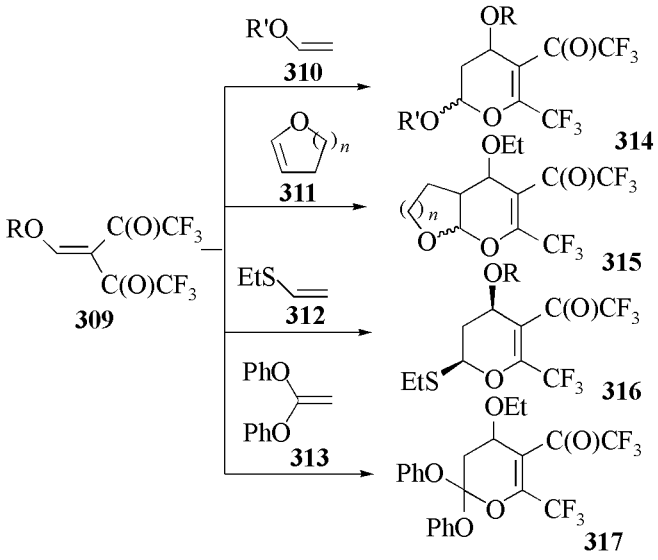
$R = CH_3, (C_2H_5)_2$.

R = Et, t-Bu; R' = Et, Ph.



compound readily suffered hydrolysis into ester **305** followed by conversion into chromone **306**. Compounds **304** exhibit hypolithidemic, anabolic, and hypoglycemic activity.

TOF as a compound supplying one carbon atom can bind three molecules of the same CH-acid by the methylene-active fragments, and then the resulting substance can be subjected to cyclization. For instance, the reaction of TOF with substituted 1,3-cyclohexanediones **307** gave rise to fused 4*H*-pyran **308** [258].



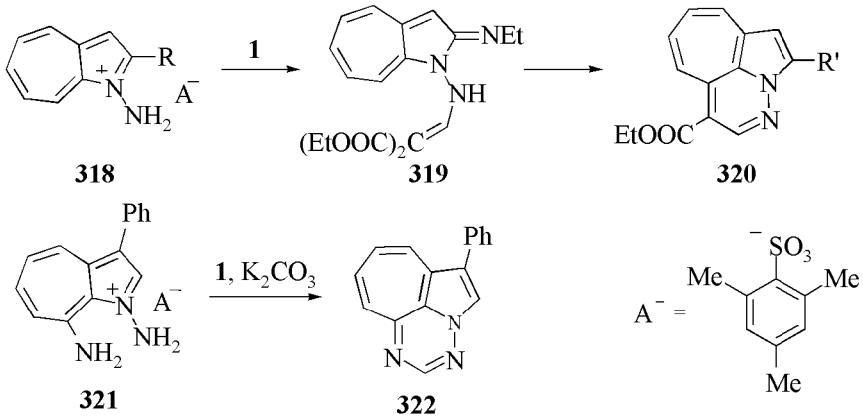
Diels–Alder heteroreaction of an active heterodiene, β,β-bis(trifluoroacetyl)vinyl ether **309** with various vinyl O- and S- derivatives **310–313** occurred without solvent predominantly with the *cis*-orientation to give cyclic adducts **314–317** [259].

Thus AOE can be applied to pyran synthesis. Therewith the building up of the pyran ring can be carried out in various ways: by substitution of an alkoxy group with a methylene-active component followed by ring closure, by electrophilic substitution of a fluorine or a hydroxy group in an aromatic ring, and also by Diels–Alder heteroreaction where the AOE plays the role of an active heterodiene. The pyran derivatives obtained attract much notice due to their potential and already found biological activity.

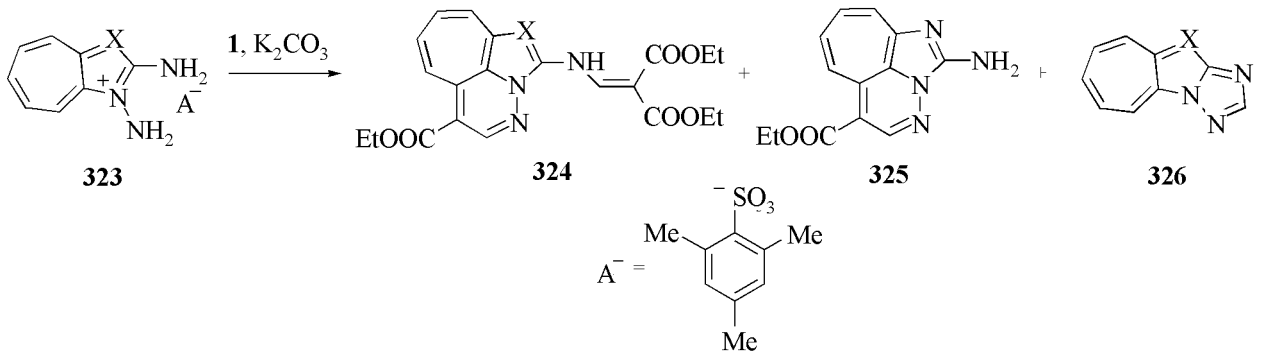
II.5. *Other Six-membered Heterocycles*

Reactions of EMME with salts of *o*-mesitylenesulfonic acid and 1-aza- and 1,3-diazaazulenium furnishing mainly various azines were studied in detail.

The reaction of salt **318** in the presence of calcium carbonate and silica gel in ethanol resulted in 92% yield of 1,2-dihydro-1-azaazulene **319** that further was converted into ethyl 2a,3-diazabenzo[*cd*]azulene-5-carboxylic acid **320** [260]. From salt of 1,8-diamino-3-phenyl-1-azaazulenium **321** and EMME that is capable as already mentioned to transfer one carbon atom fused triazine **322** was obtained [261].

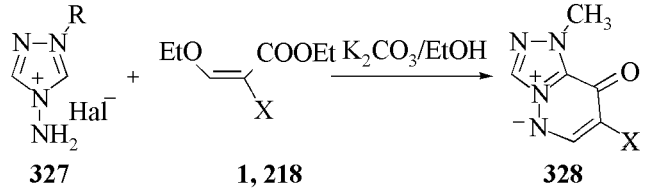


R = OMe, NHEt; R' = OEt, NHEt.



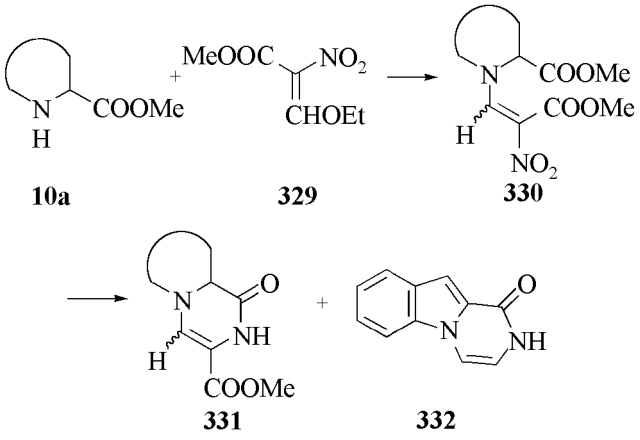
The reaction with EMME of salts of 1,2-diamino-1-aza-(1,3-diaza)-azulenium **323** in the presence of K_2CO_3 resulted in substituted benzo[*cd*]azulenes **324** and **325** and cyclopentaazulenes **326**. The products ratio depended on the solvent character. Salt **323** (X = N) afforded all three products with fused pyridazine **324** prevailing when the reaction was carried out in ethanol; in reaction performed in acetonitrile prevailed triazole **326**. Salt **323** (X = CH) gave rise in ethanol to a mixture of products **324** (12%) and **326** (50%), and in acetonitrile formed exclusively triazole **326** (96%) [262].

The treatment of 4-amino-1,2,4-triazolium salts **327** and polarized olefins **1, 218** with K_2CO_3 in ethanol provided products of reversed 1,6-cyclization, mesomeric betaines **328**, through intermediate *N*-vinyliminoylides. The attempt to isolate the latter was unsuccessful [263].



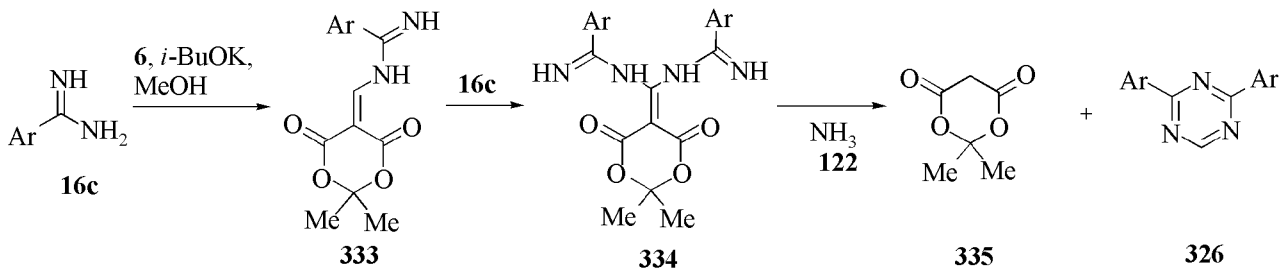
X = COOEt, NO_2; Hal = Br, I; R = Me, CH_2Ph.

The reaction of nitroalkene **329** with heterocyclic amines **10a** in MeOH/AcONa gave rise to product of S_NVin **330** which was reduced with $Mg/HgCl_2/TiCl_4$ in THF-BuOH to bicyclic pyrazinones **331** [with the ester of (DL)-indoline-2-carboxylic acid a mixture of pyrazinone **331** and its demethoxycarbonylated analog **332** was obtained] [264].



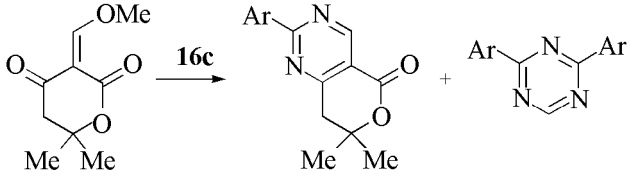
X = COOEt, NO_2; Hal = Br, I; R = Me, CH_2Ph.

We demonstrated above some examples of ring closure by a methylene bridge between two nitrogen atoms effected with the use of AOE resulting in various heterocyclic systems. Likewise an easy synthesis of 2,4-diaryl-1,3,5-triazines **336** was carried out reacting in aqueous MeOH arylamidines **16c** with AOE **6** which is also known to be capable of transferring a methylene group. It is presumed that



aminomethylene intermediate **333** added the second amidine molecule giving aminal **334** that decomposed into triazine **336** (yield 45–54%), Meldrum's acid **335**, and ammonia [265].

As was shown in the same study the C_1-building block in this reaction could be supplied also by 3-methoxymethylene-3,4-dihydropyran-2,4-diones **337**, but in this case side products, pyrano[4,3-*d*]-pyrimidines **338**, were obtained, and triazines **336** yields decreased to 30–40%.

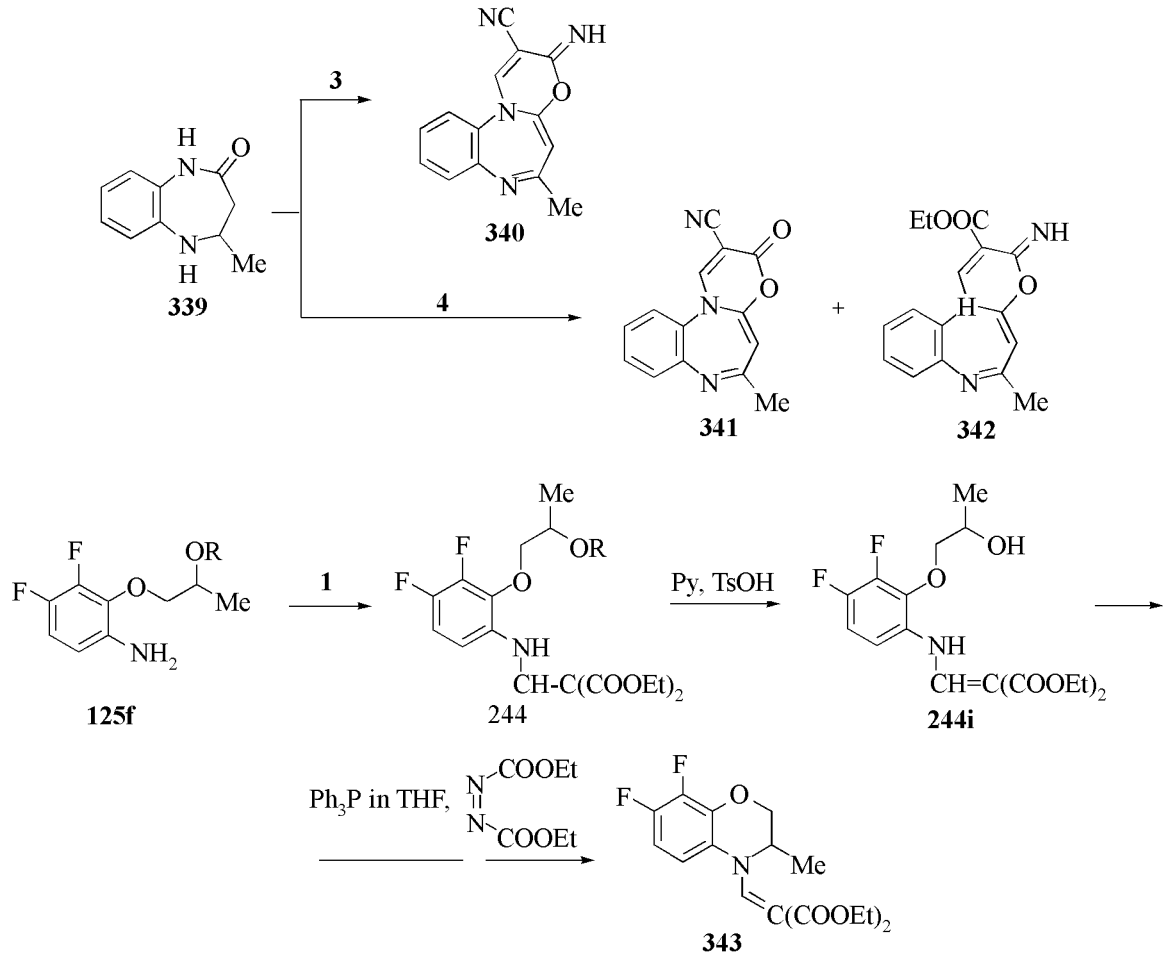


337 **338** **336**

The reaction of 4-methyl-2,3-dihydro-1,5-benzodiazepin-2(1*H*)-one **339** with EMMN and EMCA provided respectively fused 1,3-oxazines **340** or a mixture of oxazines **341** and **342** which resulted from S_NVin of ethoxy group with the nitrogen of the secondary amine **339** followed by cyclization at the carbonyl group [266].

In reaction of amine **125f** with EMME a product of S_NVin **244h** was obtained that on deprotection from tetrahydropyranyl group gave system **244i**. The latter was subjected to cyclization in the presence of diethyl azodicarboxylate and triphenylphosphine in THF to furnish benzoxazine **343** [267]. The latter serves as semiproduct in the synthesis of a bactericidal drug ofloxacin.

As seen, the synthetic methods based on AOE for preparation heterocycles not belonging to the series of pyrimidine, pyridine, or pyran are not so extensively developed. In all the examples cited the first reaction stage consists in S_NVin of alkoxy group by a nitrogen atom, and the second stage is the ring closure with participation as a rule of a functional group belonging to AOE.



R = tetrahydropyranyl group.

III. CONCLUSION

The data discussed in the review show that functionally-substituted alkoxyolefins are very attractive both for the search of new substances possessing high biological activity, and for solving the problems of fine organic synthesis. Since their alkoxy group is of excellent nucleofugic qualities they enter into reactions with various methylene-active and nirtogen-containing nucleophiles providing the corresponding products of nucleophilic substitution. Varying the functional groups attached to AOE makes possible the preparation under sufficiently mild conditions of a wide range of six-membered heterocycles possessing biological activity.

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