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SYNTHESIS OF HETEROCYCLIC COMPOUNDS USING OXALOACETIC ESTER (REVIEW)

S. A. Yamashkin and N. V. Zhukova

Published data on the use of oxaloacetic ester in the synthesis of various heterocyclic systems are discussed.

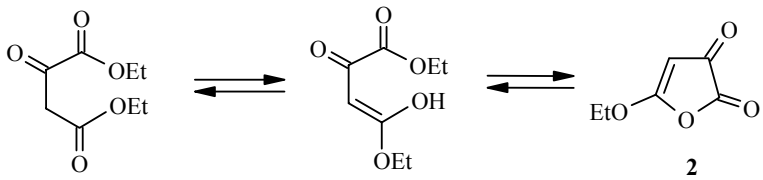
Keywords: pyrroloquinolines, quinolines, condensed heterocycles, monoheterocycles, oxaloacetic ester.

Scientists have been engaged in research on the reactions of oxaloacetic ester since the end of the nineteenth century. A large contribution to this field was made by Wislicenus, who extensively studied the chemical transformations of oxaloacetic ester [1]. The interest in oxaloacetic ester was prompted by the presence of four reaction centers in its molecule, making it possible the use it for the production of a large number of different compounds. In this review articles concerning the use of oxaloacetic ester in the synthesis of both monocyclic and condensed heterocyclic compounds are analyzed.

1. OXALOACETIC ESTER IN THE SYNTHESIS OF MONOHETEROCYCLES

There are a large number of reactions in which oxaloacetic ester is used as starting compound in the synthesis of five-membered (furan and pyrrole derivatives) and six-membered (pyridine and pyrimidine derivatives) heterocycles.

Thus, for example, oxaloacetic ester (**1**) undergoes intramolecular ester condensation, forming the dioxo derivative of furan **2** [2].



1 **2**

M. E. Evsevyev Mordovinian State Pedagogical Institute, Saransk, 430007, Russia; e-mail: biotech@moris.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 163-187, February, 2008. Original article submitted September 4, 2007.

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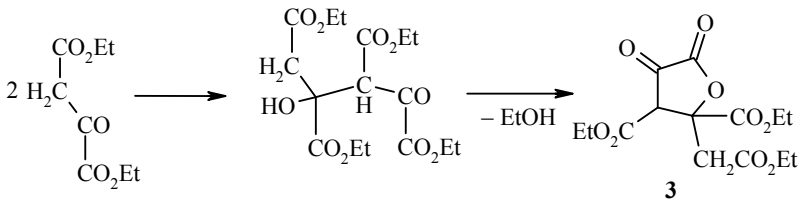
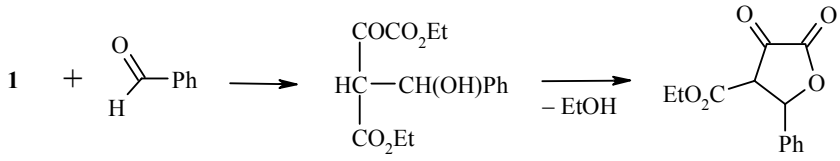
Under the action of potassium acetate two molecules of oxaloacetic ester are capable of entering into aldol condensation followed by cyclization to the furan derivative **3** [3, 4].



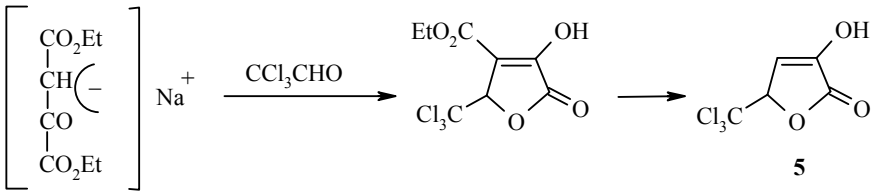
3

The reaction with benzaldehyde takes place similarly with the formation of compound **4** [4].



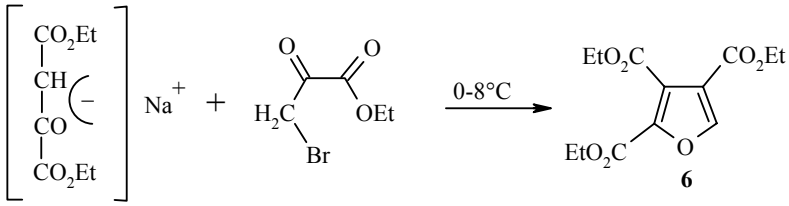
4

α-Keto-γ-trichloromethyl-γ-lactone **5** was obtained from the sodium salt of oxaloacetic ester and trichloroacetaldehyde [5].



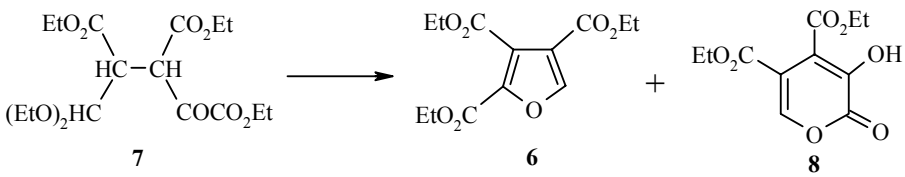
5

Triethyl 2,3,4-furantricarboxylate (**6)** was prepared from the sodium derivative of oxaloacetic ester and ethyl bromopyruvate in an alkaline medium [6].



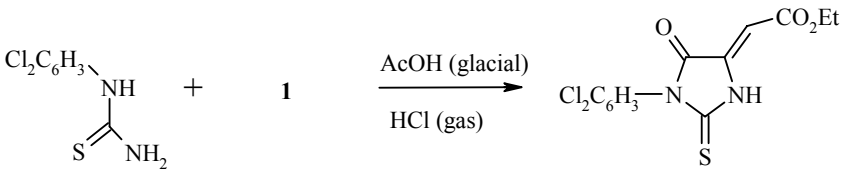
6

Compound **6** is also produced in a mixture with 4,5-diethoxycarbonyl-3-hydroxy-2-pyranone (**8**) by sulfuric acid treatment of the product **7** from the condensation of oxaloacetic ester with formyl succinate [7].



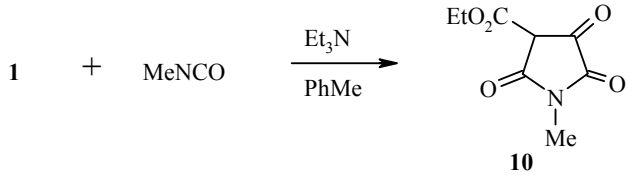
7 **6** **8**

Oxaloacetic ester is used in the synthesis of herbicides – derivatives of thiohydantoin. For example, compound **9** is an effective low-toxicity agent for weed control [8].



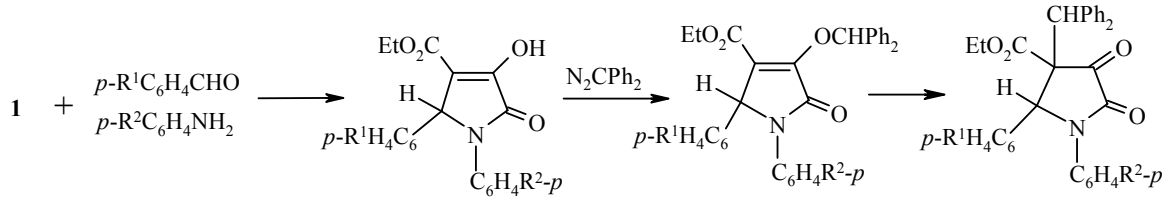
9 (77%)

The cyclocondensation of oxaloacetic ester with methyl isocyanate in the presence of triethylamine gave ethyl 1-methyl-2,3,5-trioxopyrrolidine-4-carboxylate (**10**). Analogous reactions take place successfully with other isocyanates (PhNCO, $C_{10}H_7NCO$) [9].



10

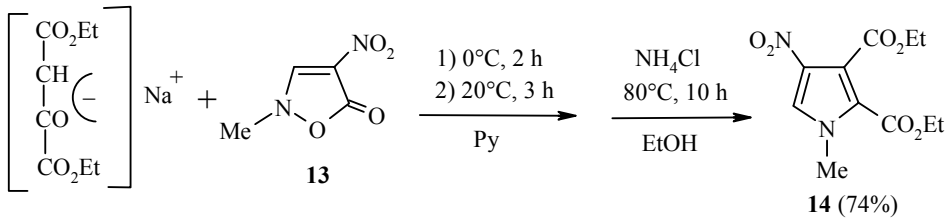
The reaction of ethyl oxaloacetate with a mixture of an aromatic aldehyde and arylamine leads to 1,5-diaryl-4-ethoxycarbonyltetrahydropyrrole-2,3-diones **11a**,**c-e**, which give O-alkylation products in reaction with diphenylazomethane. In the opinion of the authors compounds **11a**,**c-e** undergo suprasurface [1,3] sigmatropic rearrangement to 1,5-diaryl-4-ethoxycarbonyl-4-diphenylmethyltetrahydropyrrole-2,3-diones **12** when heated [10].



11a–e (28–71%) 47–88% **12a–e** (33–54%)

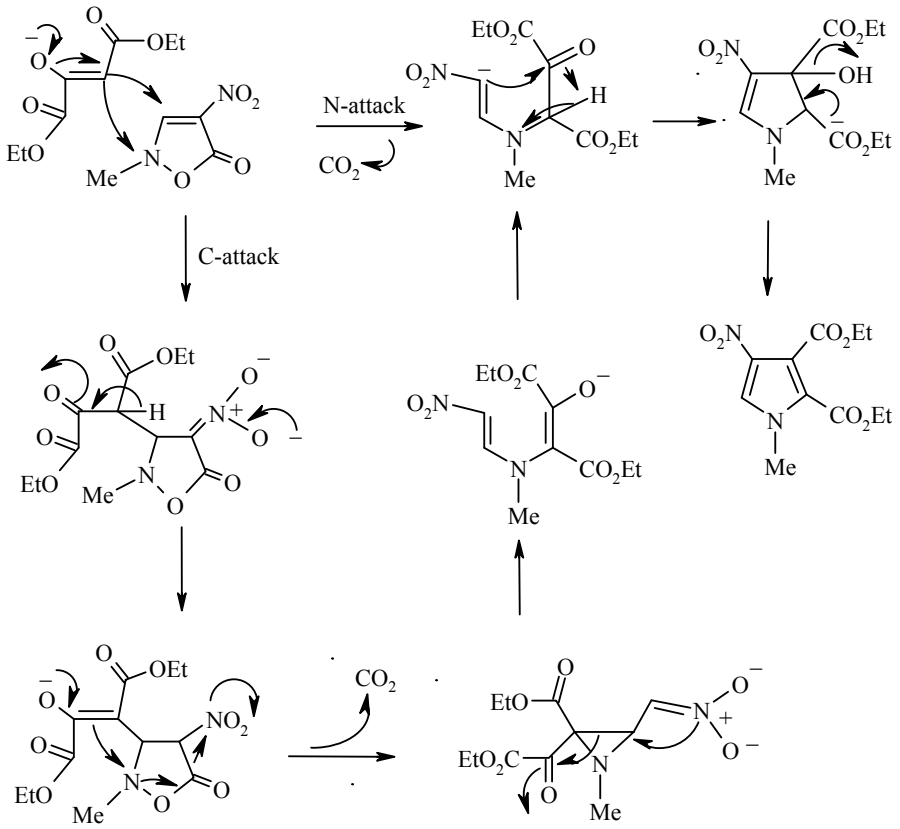
11, 12 a, e R^1 = H, **b** R^1 = Br, **c** R^1 = MeO, **d** R^1 = NO_2, **a–d** R^2 = H, **e** R^2 = NO_2

The synthesis of 2,3-bifunctional substituted 4-nitropyrroles can be achieved by the reaction of the isoxazolone **13** with various β-keto esters. If the sodium salt of oxaloacetic ester is used as β-keto ester, 2,3-diethoxycarbonyl-1-methyl-4-nitropyrrole (**14)** is formed [11].

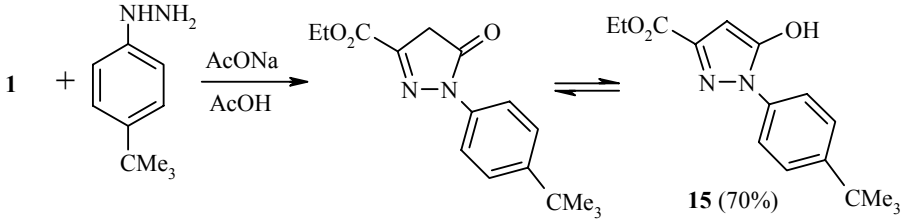


13 **14** (74%)

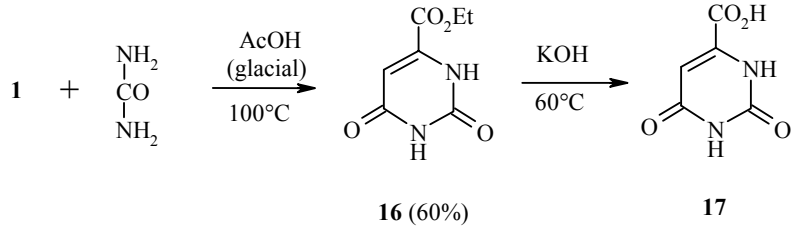
The authors proposed the following scheme for the reaction.



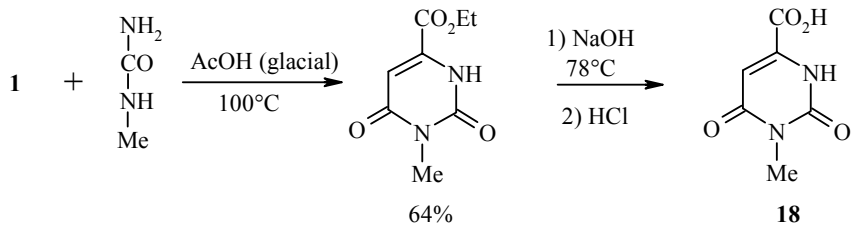
If oxaloacetic ester is used in a reaction with a substituted hydrazine compound **15** is obtained [12] in the keto and enol forms (1:1).



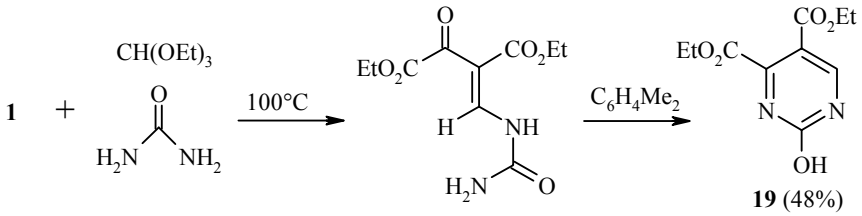
The ester **16** is readily formed during the condensation of oxaloacetic ester and urea, and its alkaline hydrolysis leads to orotic acid (2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid) (**17)** [13, 14].



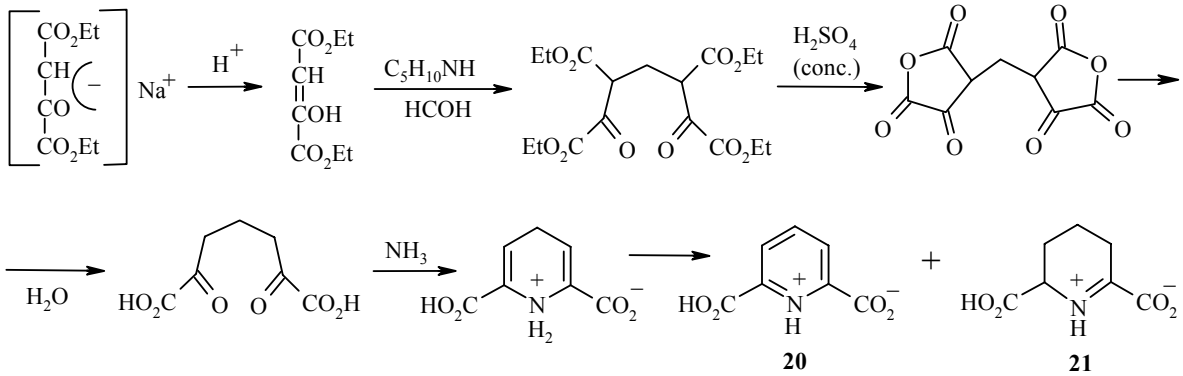
If N-methylurea is used, the N-methyl derivative of orotic acid 1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid (**18)** is obtained [15].



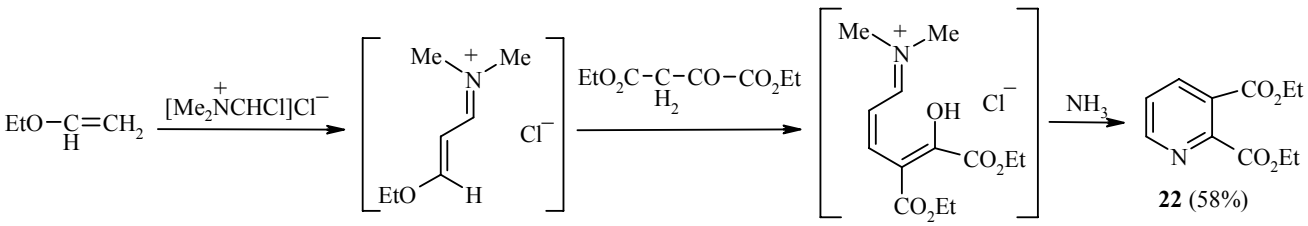
The analogous cyclocondensation of oxaloacetic ester with urea in the presence of orthoformic ester leads to the formation of diethyl 2-hydroxypyrimidine-4,5-dicarboxylate (**19)** [16, 17].



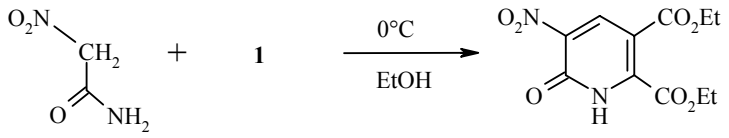
Oxaloacetic ester is also used in the synthesis of 2,3,4,5-tetrahydropicolinic acid – an intermediate in the synthesis of the enzyme L-lipase. In reaction with formaldehyde it finally forms a mixture of compounds **20** and **21** [18].



Pyridine-2,3-dicarboxylic acid and its derivatives are biologically active compounds. American scientists proposed and patented an effective method for the synthesis of diethyl pyridine-2,3-dicarboxylate (**22)** based on the successive reaction of ethyl vinyl ether with the Vilsmeier reagent, oxaloacetic ester, and a source of ammonia [19].

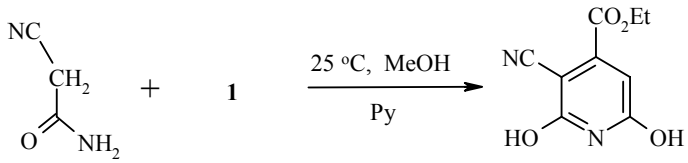


The reaction of oxaloacetic ester with nitroacetamide in absolute alcohol at 0°C leads to the formation of diethyl 1,6-dihydro-5-nitro-6-oxo-2,3-pyridinedicarboxylate (**23**) [20].



23 (78%)

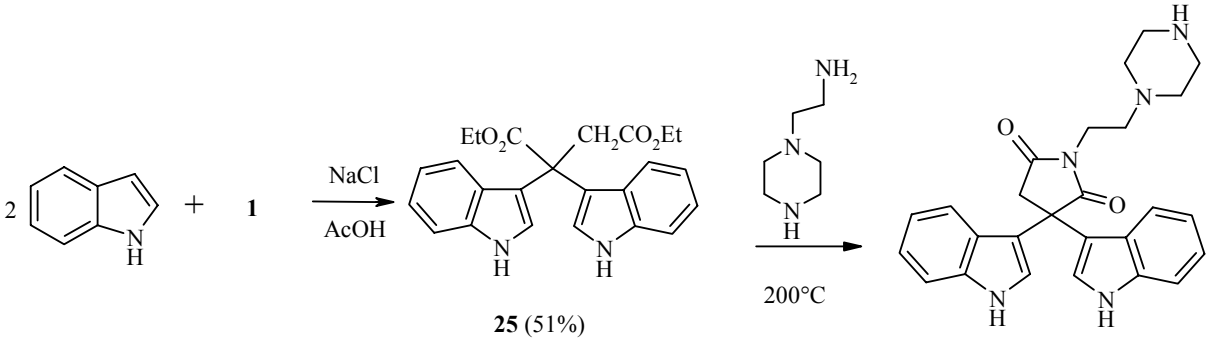
If cyanoacetamide is used in this reaction 3-cyano-4-ethoxycarbonyl-2,6-dihydroxypyridine (**24**) is obtained [21].



24 (36%)

Oxaloacetic ester reacts readily with unsubstituted indoles. The reaction is similar to the condensation of indole with pyruvic acid. If oxaloacetic ester is heated with two moles of indole in a solution of common salt in acetic acid compound **25** is formed [22].

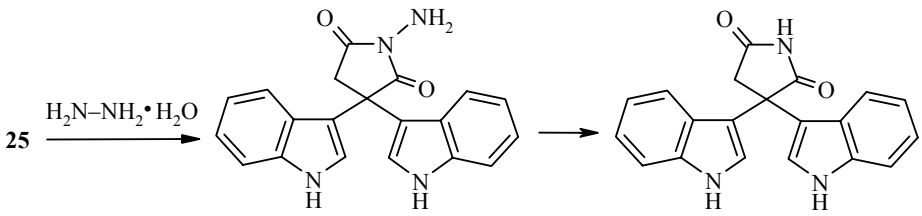
N-(2-Piperazinoethyl)-3,3-di(1H-indol-3-yl)succinimide (**26**) was obtained by heating compound **25** in N-(2-aminoethyl)piperazine.



25 (51%)

26 (82%)

In addition, when heated with hydrazine hydrate in a stream of nitrogen, compound **25** forms N-amino-3,3-di(1H-indol-3-yl)succinimide (**27**), which is reduced by hydrazine hydrate in dioxane in the presence of Raney nickel to 3,3-di(1H-indol-3-yl)succinimide (**28**).



27 (78%)

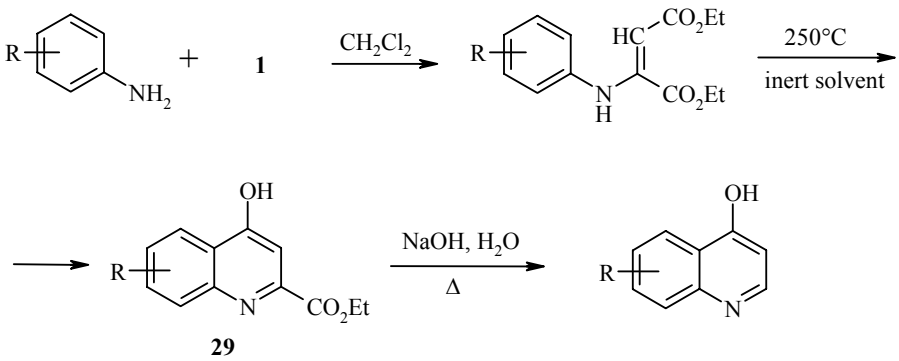
28 (58%)

2. OXALOACETIC ESTER IN THE SYNTHESIS OF CONDENSED HETEROCYCLES

2.1. Production of Quinoline Systems from Arylamines and Oxaloacetic Ester under the Conditions of the Conrad–Limpach Reaction

Widely differing amines have been used in condensations with β-keto esters in modifications of the Conrad–Limpach and Knorr methods for the synthesis of quinolines [23-25].

2-Ethoxycarbonyl-4-hydroxyquinolines **29** are formed readily from oxaloacetic ester as the β-keto ester component in the Conrad–Limpach synthesis, and their hydrolysis and decarboxylation lead to 4-hydroxyquinolines [23].

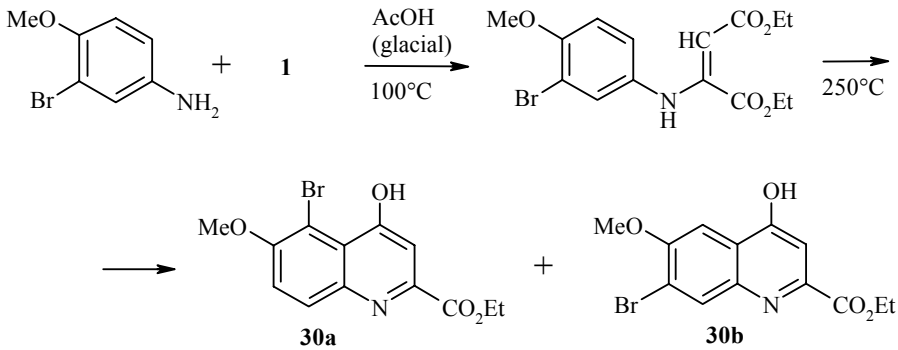


29

This method gives high yields under conditions depending on the nature of the substituents in the benzene ring. Many of the obtained acids can be decarboxylated in an inert solvent at ~250-270°C. However, in the presence of electron-accepting substituents like the nitro group decarboxylation is better realized by heating the silver salts of the acids (with poor yields).

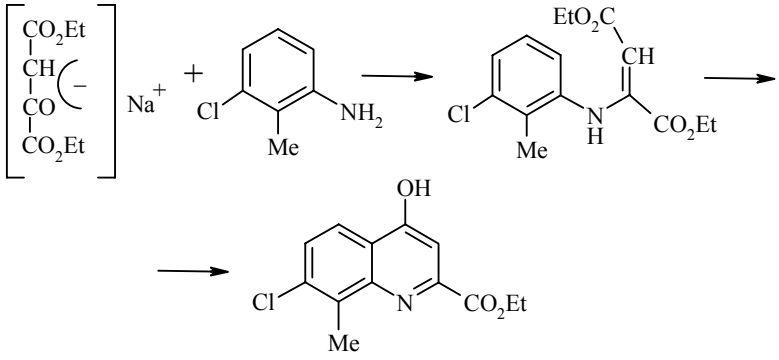
As expected, if *meta*-substituted anilines are heated with oxaloacetic ester a mixture of 5- and 7-substituted quinolines is formed. The ratio of the esters of 5- and 7-chloroquinoline-2-carboxylic acids, obtained from *m*-chloroaniline, varies from approximately 12:1 (if the ratio of the inert solvent and the initial condensation product in the reaction mixture at the thermal cyclization stage is 1:1) to 0.4:1 (if a dilution of 30:1 is used during cyclization). The ratio of the isomers is evidently affected by steric factors.

A mixture of the ethyl esters of 5-bromo- (**30a**) and 7-bromo-4-hydroxy-6-methoxyquinoline-2-carboxylic acids (**30b**), which can be separated by crystallization from methanol, is formed during the condensation of 3-bromo-4-methoxyaniline with oxaloacetic ester followed by cyclization of the intermediately formed enamine [26].



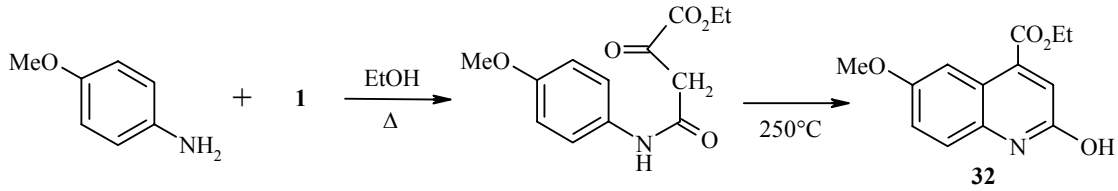
30a **30b**

Of course, if there is only one vacant site for cyclization in the substituted aniline substrate only 4-hydroxyquinoline is formed with a high yield. For example, the yield of 7-chloro-2-ethoxycarbonyl-4-hydroxy-8-methylquinoline (**31**), produced by the condensation of sodiooxaloacetic ester with 3-chloro-2-methylaniline, approaches 90% [27].



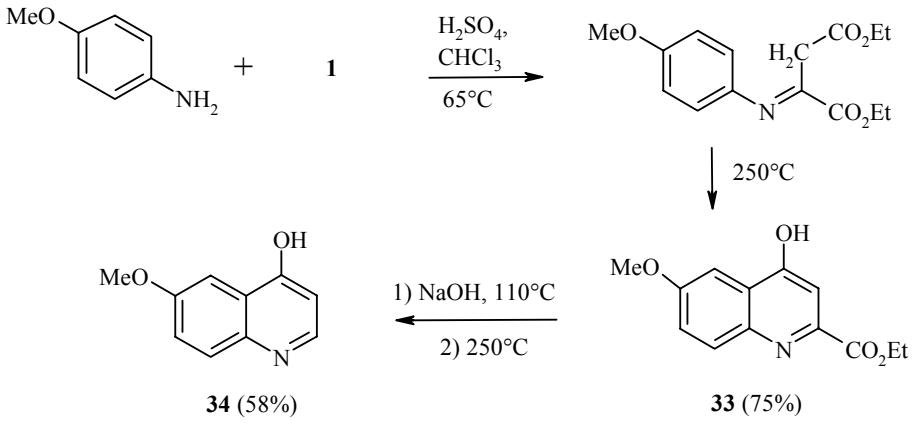
31 (89%)

However, the formation of enamines is not the only path in the reaction of oxaloacetic ester with aromatic amines. The presence of the ester group still suggests the possibility of the formation of amides, the subsequent cyclization of which should lead to isomeric 2-hydroxyquinolines. According to data in [23], such a reaction path is realized when an alcohol solution of *p*-anisidine is boiled with oxaloacetic ester. In this case ethyl 2-hydroxyquininate **32** is formed.



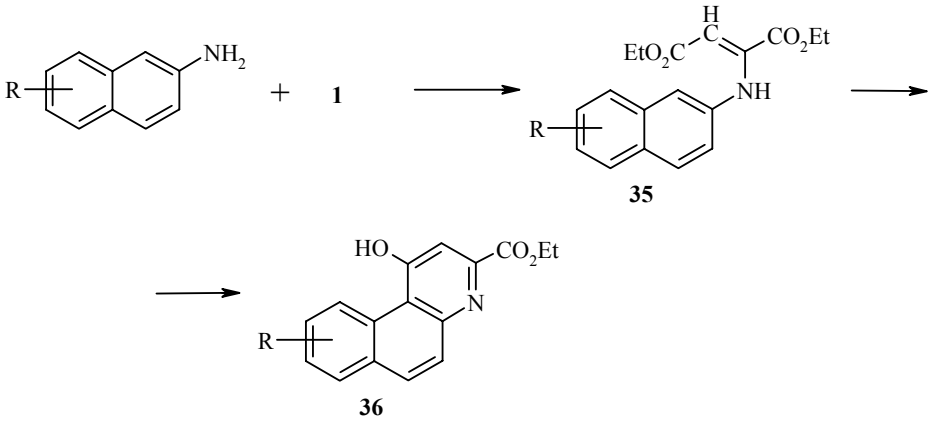
32

By changing the conditions in the condensation of *p*-anisidine with oxaloacetic ester (heating in chloroform in the presence of sulfuric acid) it is possible to direct the reaction toward the formation of the imine, the subsequent cyclization of which in dowtherm leads to the formation of 2-ethoxycarbonyl-4-hydroxy-6-methoxyquinoline (**33**). Hydrolysis of the ester **33** with sodium hydroxide followed by decarboxylation at 250°C gives compound **34** [28].

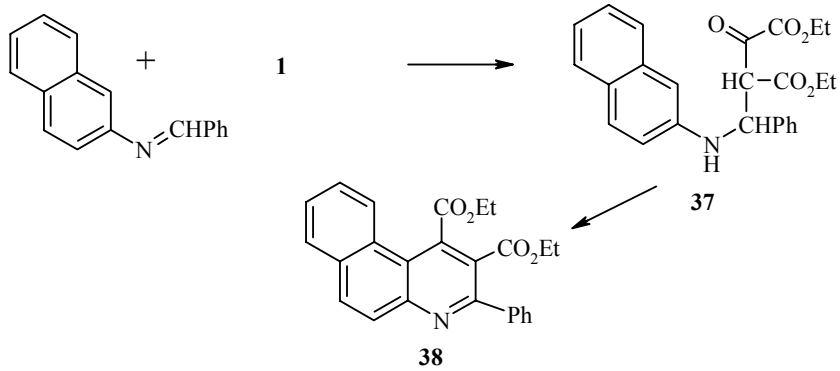


34 (58%) **33** (75%)

If condensed aromatic amines are brought into reaction with oxaloacetic ester it is possible to synthesize tricyclic compounds. For instance, there is a method for the production of derivatives of 4-hydroxybenzoquinolines **36** with an ethoxycarbonyl group at position 2 by using 2-naphthylamine as the aromatic amine component [23].

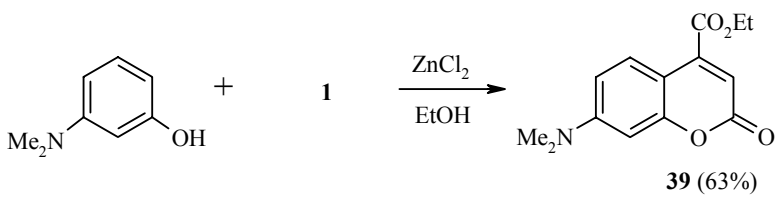


Oxaloacetic ester can be regarded as a carboxylated pyruvic ester, which can enter into a Doebner "pyruvic synthesis." Thus, it was found that benzylidene-β-naphthylamine readily adds oxaloacetic ester with the formation of compound **37**, which undergoes cyclization to the corresponding benzoquinoline **38** [23].

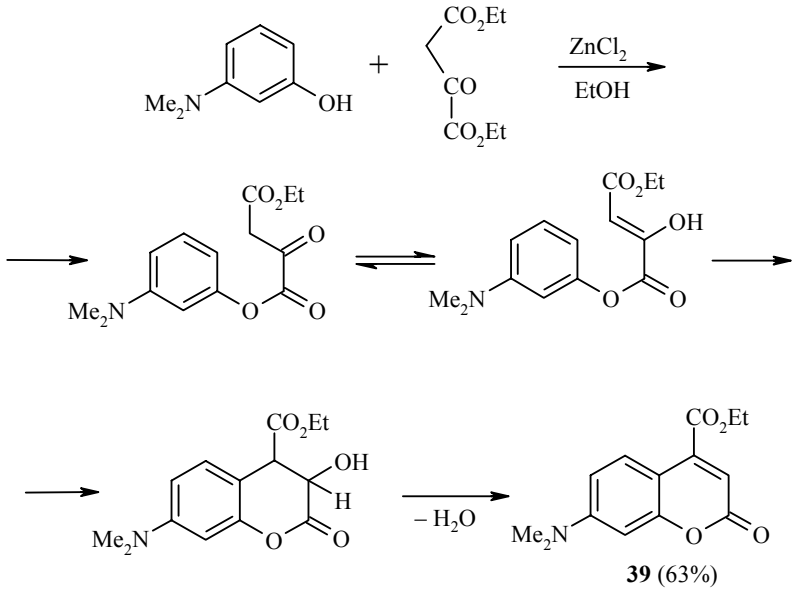


Various arylidene derivatives of naphthylamine can be used in the reaction. Thus, β-naphthylamine also gives the corresponding benzoquinoline in reaction with *m*-nitrobenzaldehyde and oxaloacetic ester.

The possibilities of using oxaloacetic ester in the synthesis of various heterocycles are significantly extended as a result of its ability to react not only with anilines but also with phenols. Thus, ethyl 7-dimethylaminocoumarin-4-carboxyliate (**39**) is formed in the reaction with 3-dimethylaminophenol in the presence of anhydrous zinc chloride [29].



It can be supposed that the reaction takes place according to the following scheme:

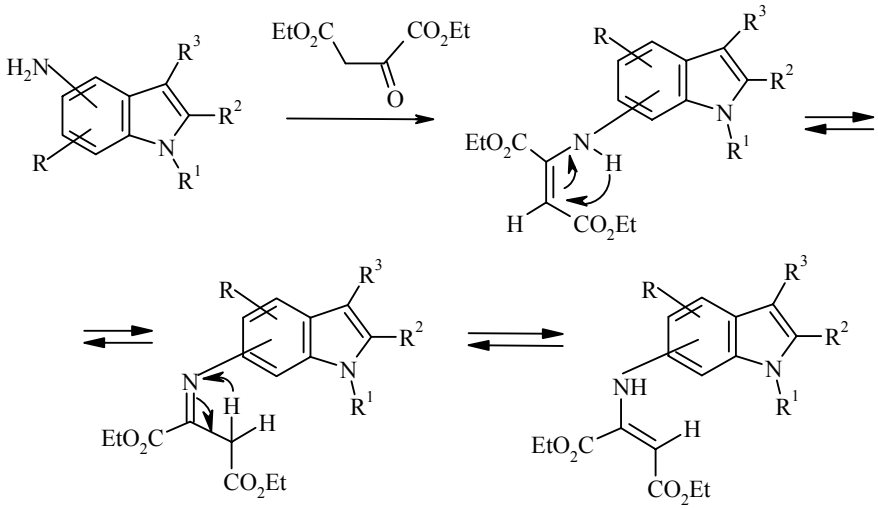


39 (63%)

2.2. Production of Quinoline Systems from Aminoindoles and Oxaloacetic Ester under the Conditions of the Conrad–Limpach Reaction

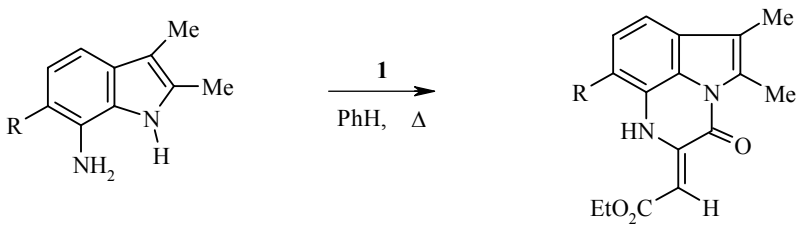
2.2.1 Condensation of Substituted 4-, 5-, 6-, and 7-Aminoindoles with Oxaloacetic Ester. The presence of three reaction centers in the oxaloacetic ester molecule predetermines the formation of both the product from condensation at the carbonyl group (the enamine) and two possible amides at the two ester groups in the initial stage of the reaction. For aminoindoles unsubstituted at the β-position of the pyrrole ring the possibility of condensation at this position is not ruled out.

However, the authors of [30-34] established that oxaloacetic ester reacts with aminoindoles in boiling benzene at the carbonyl group with the exclusive formation of the corresponding enamines. In a number of cases the isomeric and tautomeric forms are observed in the solution.



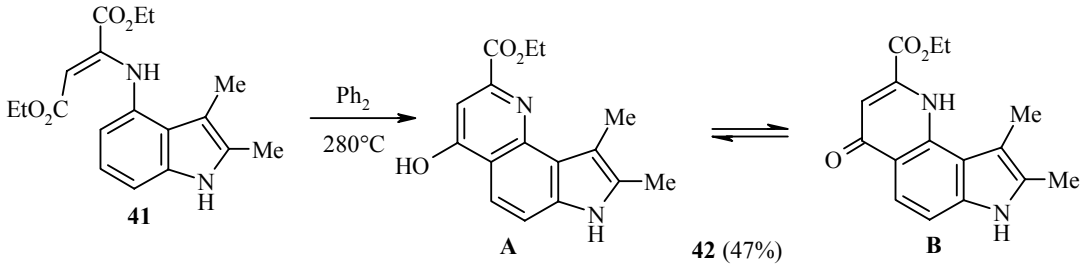
4-, 5-, 6-, 7-NH(N=); R = H, Me, OMe; R^1 = H, Me; R^2 = Me, Ph; R^3 = H, Me

Only for 7-aminoindoles unsubstituted at the pyrrole nitrogen atom does the reaction with oxaloacetic ester lead to the formation of pyrroloquinoxalines **40a**,**b** [33, 34].

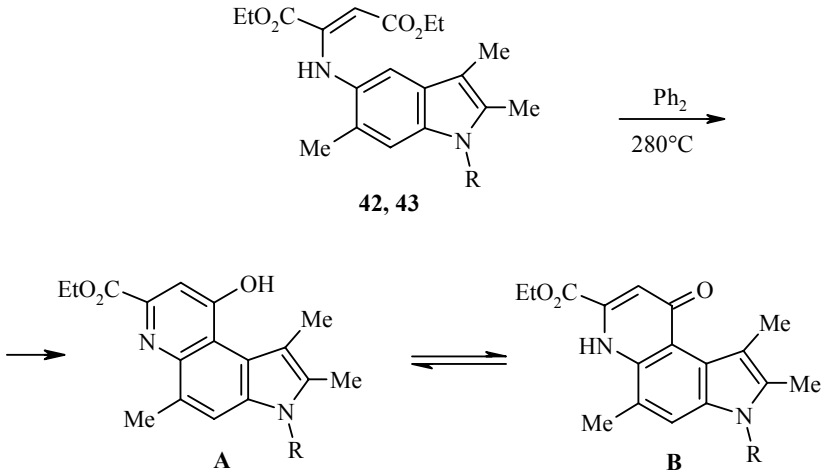


40 a R = H (23%), **b** R = OMe (15%) **40a,b**

2.2.2. Synthesis of Pyrrolo[2,3-*h*]quinolines. In boiling biphenyl the product **41** from the condensation of 4-amino-2,3-dimethylindole with oxaloacetic ester is transformed into the pyrroloquinoline **42**, the ^{1}H NMR spectra of which in DMSO-d_6 indicate the presence of two tautomeric forms, the hydroxyquinoline (**A**) and quinoline (**B**) forms in a ratio of 3:1 (according to the integral intensity of the protons).



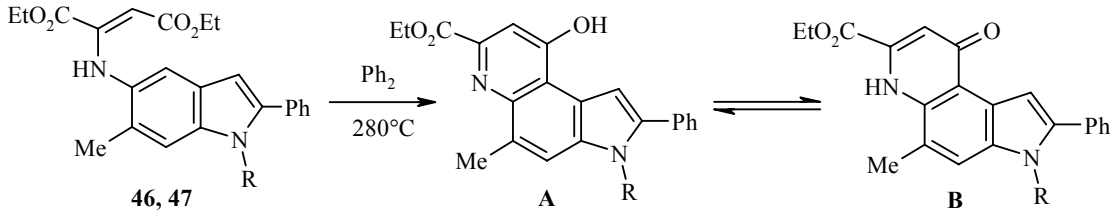
2.2.3. Synthesis of Pyrrolo[3,2-*f*]quinolines. When heated in biphenyl at 280°C for 20 min the (5-indolyl)amino derivatives of diethyl fumarate (the enamines **42** and **43**) condense to the pyrroloquinolines **44** and **45**, which in DMSO-d_6 solution exist predominantly in form **A**.



44 (81%); **45** (66%); **A : B** = 7:1

42, **44** R = H; **43**, **45** R = Me

The pyrrolo[3,2-*f*]quinolines **48** and **49** with an α-phenyl group in the pyrrole ring were obtained by thermal cyclization of the corresponding enamines **46** and **47**.

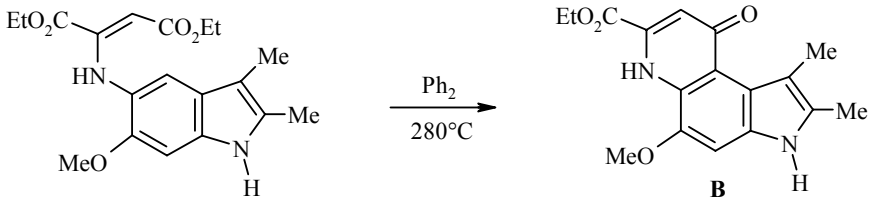


48 (57%); **49** (41%); **A : B** = 8:1

46, 48 R = H; **47, 49** R = Me

Thus, the nature of the substituent (Me, H) at position 1 does not have a significant effect on the ratio of forms **A** and **B** of the obtained pyrroloquinolines.

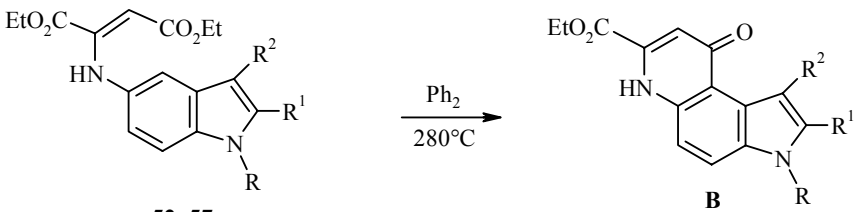
On the other hand the nature of the substituent at position 6 of 5-aminoindole has a significant effect on the preferential formation of the cyclization product in one or the other tautomeric form. Thus, replacement of the methyl group in the initial compound by a methoxyl group (the enamine **50**) leads to the exclusive production of pyrroloquinolone with the angular structure **51** (form **B**).



51 (32%)

By using the enamines **52-57** unsubstituted in the benzene ring in thermal cyclization reactions it is possible to determine the direction of annulation of the pyridine ring at the two alternative free positions to the amino group in the benzene ring of the indole bicycle and also the effect of the size of the substituent on the formation of the angular ([3,2-*f*]) and linear ([2,3-*g*]) pyrroloquinoline systems.

Thus, by virtue of the steric factors it must be expected that the enamines unsubstituted at position 3 should undergo cyclization at the C-4 atom with the formation of the corresponding pyrrolo[3,2-*f*]quinolines. Actually, when heated in biphenyl compounds **52-57** are converted into the pyrroloquinolines **58-63**, which in DMSO-d_6 exist in the quinolone form **B**.



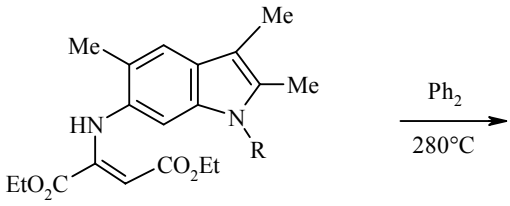
52, **58** R = R^2 = H, R^1 = Me (69%); **53**, **59** R = R^1 = Me, R^2 = H (41%);
54, **60** R = R^2 = H, R^1 = Ph (76%); **55**, **61** R = Me, R^1 = Ph, R^2 = H (95%);
56, **62** R = H, R^1 = R^2 = Me (84%); **57**, **63** R = R^1 = R^2 = Me (54%)

If the steric requirements of the substituents at the β-position of the pyrrole ring of the enamine, which prevent cyclization at position 4 of indole, are increased it could be expected that pyrroloquinolines with linear fusion of the rings would be produced. However, the enamines **56** and **57** produced from 5-amino-2,3-dimethyl- and 5-amino-1,2,3-trimethylindoles and oxaloacetic ester under the conditions of thermal cyclization, like all the preceding compounds, are transformed unambiguously into the angular pyrroloquinolines **62** and **63**, for which form **B** is also fixed.

Thus, irrespective of the nature of the substituent (H, Me, Ph) in the pyrrole part of the molecule, the enamines **52-57** are converted under the conditions of thermal cyclization into the corresponding pyrrolo-[3,2-*f*]quinolines, which exist predominantly or exclusively in form **B**.

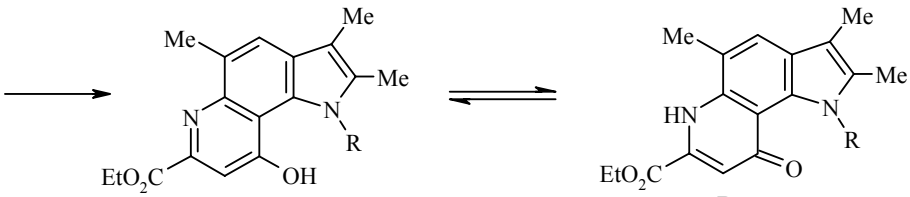
2.2.4. Synthesis of Substituted Pyrrolo[2,3-*f*]quinolines. The high-temperature behavior of compounds **64-67**, obtained from 6-amino-5-methyl- and 6-amino-5-methoxy-2,3-dimethyl- and 6-amino-1,2,3-trimethylindoles and oxaloacetic ester, was investigated in order to develop specific methods for the synthesis of pyrrolo-[2,3-*f*]quinolines with an α-ethoxycarbonyl-containing γ-quinolone fragment, which are structural analogs of vitamin PQQ – 2,7,9-tricarboxy-1H-pyrrolo[2,3-*f*]quinoline-4,5-dione. Thermal cyclization of the enamine **64** in boiling biphenyl leads to the production of pyrrolo[2,3-*f*]quinoline **68**, for which both forms (**A**, **B**) were established in an approximately equal ratio [32].

The N-methylenamine **65** also readily undergoes thermal cyclization irrespective of some steric hindrance to attack at position 7. Here too a mixture of forms **A** and **B** is observed for the pyrroloquinoline **69**.

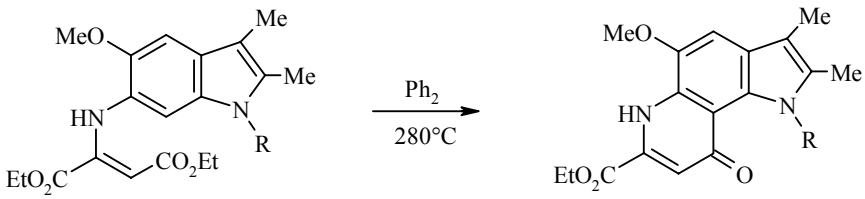


64, 65

64, 68 R = H (58%); **65, 69** R = Me (57%)



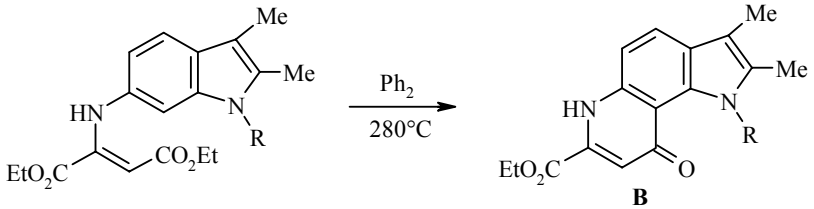
The pyrroloquinolines **70** and **71** are formed from 5-methoxyenamines **66** and **67** with somewhat greater difficulty, as seen from the longer reaction time.



66, 67 **70, 71**

66, 70 R = H (96%); **67, 71** R = Me (67%)

During the thermolysis of the enamines **72** and **73** with two free positions (5, 7) to the amino group the authors did not rule out the possibility of formation of a mixture of pyrroloquinolines with linear and angular structure. However, compound **72** undergoes exclusive cyclization to the angular pyrroloquinoline **74**.



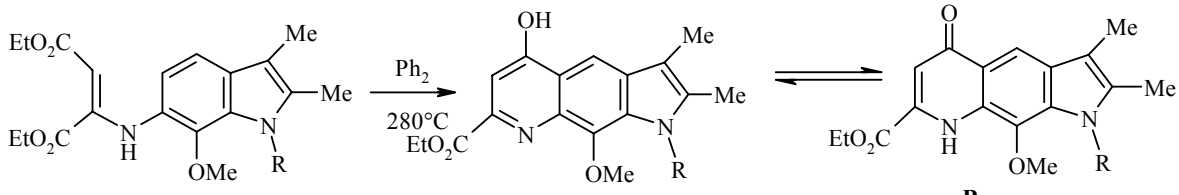
72, 73 **B** **74, 75**

72, 74 R = H (80%); **73, 75** R = Me (64%)

The introduction of a methyl substituent to the pyrrole nitrogen atom in order to create steric hindrances for attack at position 7 does not change the direction of ring formation. The enamine **73** is also transformed into the corresponding pyrrolo[2,3-*f*]quinolone **75**.

Thus, under the conditions of thermal cyclization the enamines **64-67**, **72**, and **73**, obtained from both 5-substituted and unsubstituted 6-aminoindoles and oxaloacetic ester, are transformed into pyrrolo-[2,3-*f*]quinolines. The nature of the substituents at the pyrrole nitrogen atom also does not affect the direction of closure of the pyridine ring.

2.2.5. Synthesis of Substituted Pyrrolo[3,2-*g*]quinolines. In order to synthesize pyrrolo[3,2-*g*]quinolines with linear fusion of the rings the authors of [32] used the enamines **76** and **77**, obtained from 6-amino-7-methoxy-2,3-dimethyl- and 6-amino-7-methoxy-1,2,3-trimethylindoles and oxaloacetic ester, as substrates. Here two pyrrolo[3,2-*g*]quinolines **78** and **79**, for which the form **A** was mostly identified in DMSO-d_6, were isolated.

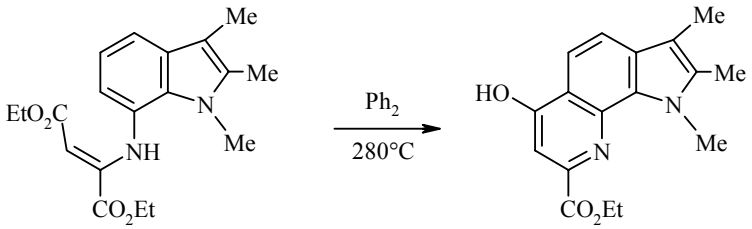


76, 77 **A** **78, 79** **B**

76, 78 R = H (61%); **77, 79** R = Me (76%)

Thus, the pyrrolo[3,2-*g*]quinoline system is only formed readily from 7-substituted 6-aminoindoles with the participation of oxaloacetic ester.

2.2.6. Synthesis of Substituted Pyrrolo[3,2-*h*]quinoline. Diethyl indolylaminofumarate **80** undergoes cyclization when heated in biphenyl (280°C) with the formation of pyrrolo[3,2-*h*]quinoline **81** [33, 34].



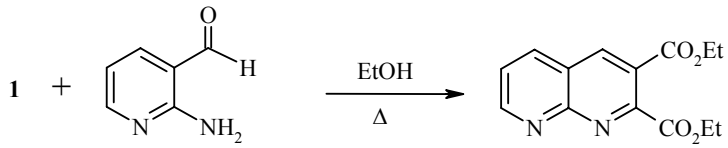
80 **A**

81 (56%)

3. PRODUCTION OF CONDENSED HETEROCYCLES WITH TWO OR MORE HETEROATOMS

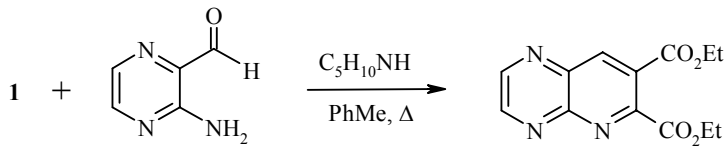
Many heterocyclic diesters that are natural compounds can be obtained synthetically from amino- or enaminoheterocycles and oxaloacetic ester. Amino-substituted heterocycles having at least one free *ortho* position or a substituent suitable for cyclization readily condense with oxaloacetic ester. For example, diethyl pyridine-2,3-dicarboxylates can be obtained by the condensation of the corresponding amines with oxaloacetic ester by boiling in an inert solvent for 24 h (78°C) [20].

This method can also be used successfully for the production of heterocyclic systems with several heteroatoms. Thus, diethyl 1,8-naphthiridine-2,3-dicarboxylate (**82)** is readily obtained by boiling 2-amino-3-formylpyridine with oxaloacetic ester in absolute ethanol for 20 h [20].



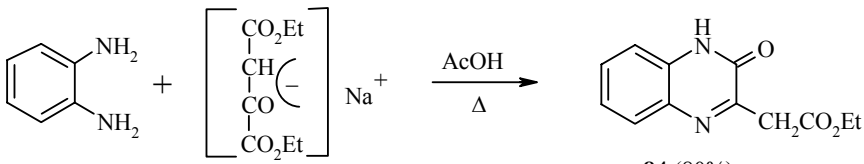
82 (62%)

However, if 3-amino-2-formylpyrazine is used in the reaction diethyl pyrido[2,3-*d*]pyrazine-6,7-dicarboxylate (**83**) is produced by boiling in toluene with the addition of piperidine [20].



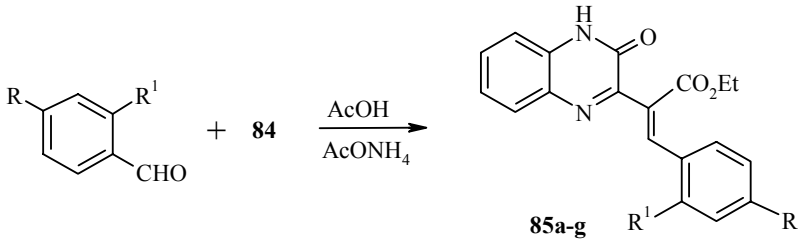
83 (58%)

The cyclocondensation of oxaloacetic ester with *o*-diamines is a convenient method for the synthesis of various quinoxalines. Thus, when 1,2-diaminobenzene is boiled with the sodium salt of oxaloacetic ester in acetic acid for 2 h ethyl quinoxaline-3(4H)-on-2-ylacetate (**84**) is obtained [35].



84 (80%)

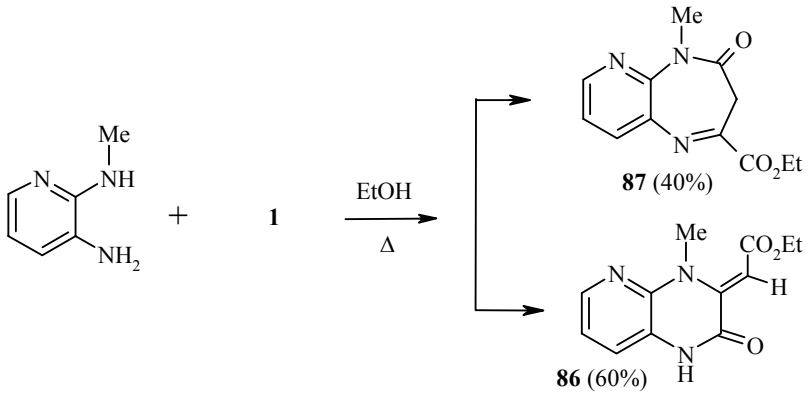
The vinyl derivatives **85a-g**, which are used for the production of polyester fibers, are easily obtained as a result of this reaction between quinoxaline and 4-alkylaminobenzaldehydes.



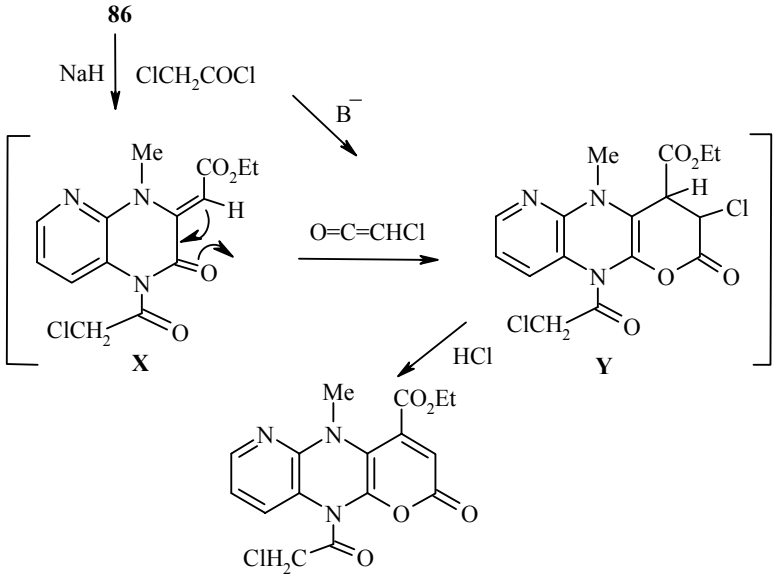
85a-g

85 a R = NMe_2, R^1 = H (75%); **b** R = NMe_2, R^1 = OMe (70%); **c** R = NEt_2, R^1 = OMe (72%); **d** R = NEtPh, R^1 = H (80%); **e** R = OMe, R^1 = H (80%); **f** R = NO_2, R^1 = H (75%); **g** R = NHCOMe, R^1 = H (75%)

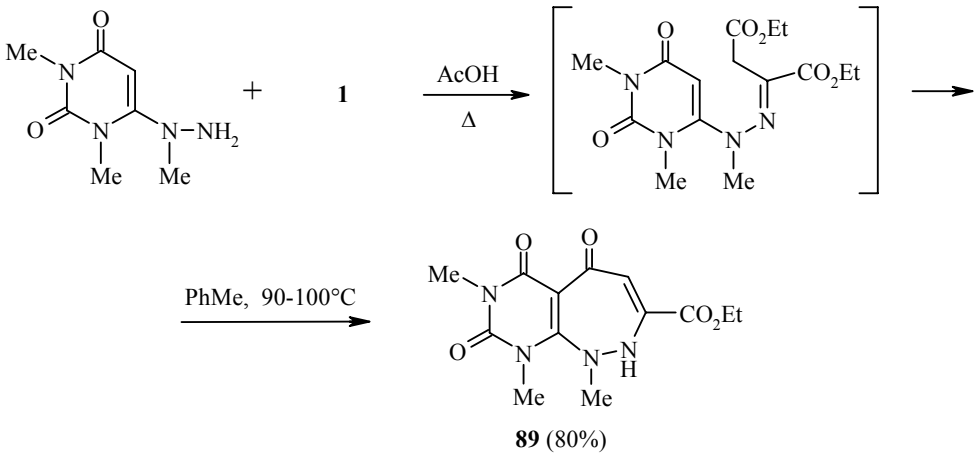
When heated with oxaloacetic ester in ethanol for 12 h 3-amino-2-methylaminopyridine forms a mixture of ethyl [2(1H)-oxo-5-azaquinoxalin-3(4H)-ylidene]acetate (**86**) and 2-ethoxycarbonyl-5-methyl-3,4-dihydro-5H-pyrido[2,3-*b*][1,4]diazepin-4-one (**87**) [36].



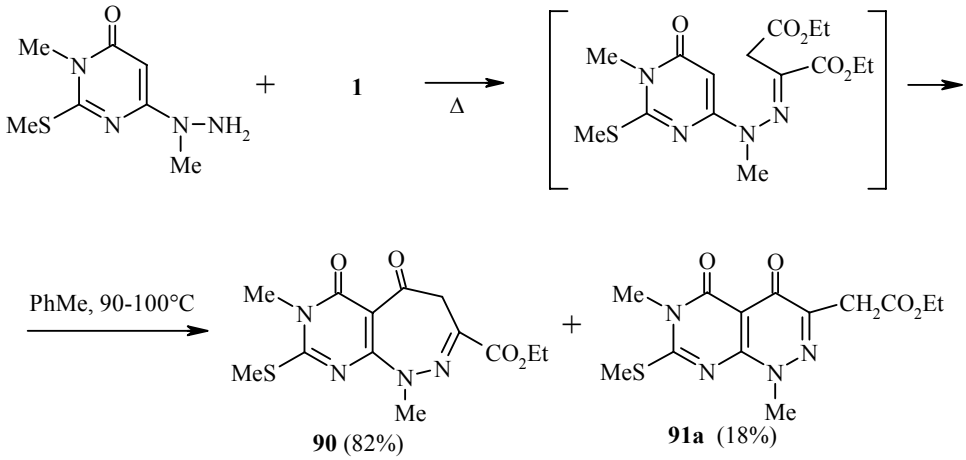
Compound **86** can then react with chloroacetyl chloride in the presence of sodium hydride in toluene with heat, leading to the formation of 10-chloroacetyl-4-ethoxycarbonyl-5-methyl-5,10-dihydro-2H-pyrano-[2,3-*b*]pyrido[2,3-*e*]pyrazin-2-one (**88**). The authors suggest that this process probably takes place in the following way: The chloroacetyl chloride acylates compound **86** in the presence of sodium hydride with the formation of the intermediate **X**; the basic medium then catalyzes the formation of chloroketene, which participates in cyclocondensation with the formation of the intermediate **Y.** Subsequent elimination of hydrogen chloride leads to compound **88**.



The reaction of oxaloacetic ester with various hydrazines forms the basis of the construction of seven-membered diazepine structures. Thus, the product from the condensation of 1,3-dimethyl-6-methylhydrazinouracil and oxaloacetic ester readily undergoes cyclization when heated in toluene and forms dihydropyrimidodiazepinetrione **89**. In the case of 6-methylhydrazino-2-methylthiopyrimidine, together with the formation of the diazepinedione **90**, there is the alternative possibility of cyclocondensation with the formation of the six-membered pyridazine structure **91a** [37].



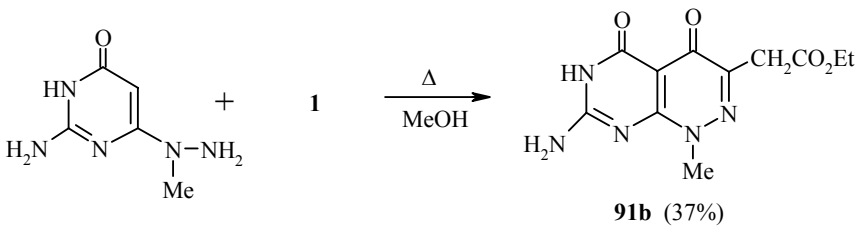
89 (80%)



90 (82%) **91a** (18%)

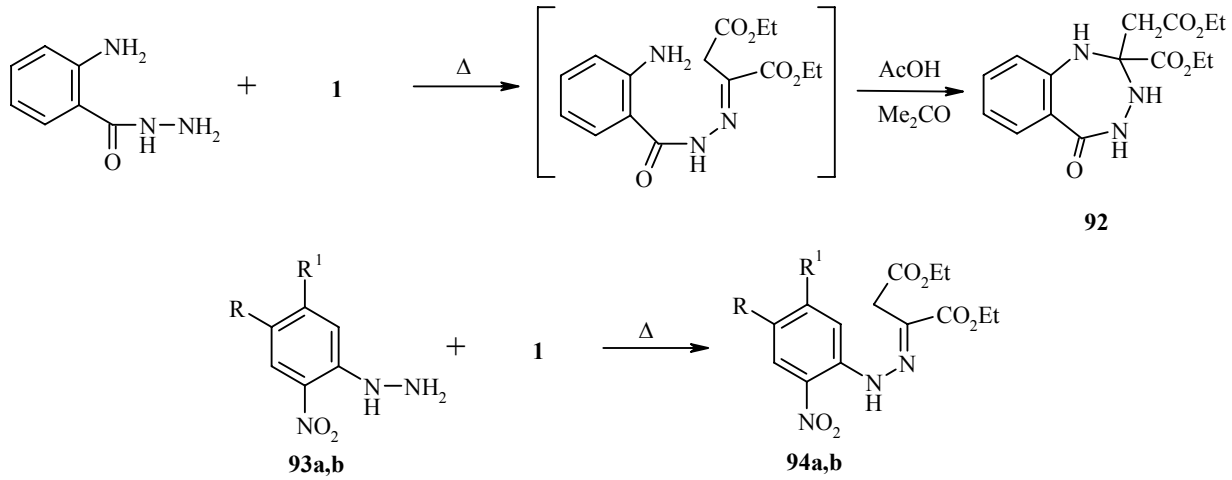
Analogous results were obtained when dimethyl oxaloacetate was used [38].

The synthesis of pyrimido[4,5-*c*]pyridazines by the cyclization of α-keto esters with 6-(1-alkylhydrazino)isocytosines was described in [39]. Oxaloacetic ester was also used as α-keto ester. 7-Aminopyrimido-[4,5-*c*]pyridazine-4,5(1H,6H)-dione **91b** is formed as a result of heating the initial substances in methanol for 48 h.



91b (37%)

The triazepine derivative **92** can be obtained from anthranilohydrazide [40], whereas only the corresponding 2-nitrophenylhydrazones **94a**,**b** are formed from substituted 2-nitrophenylhydrazines **93a**,**b** [41].

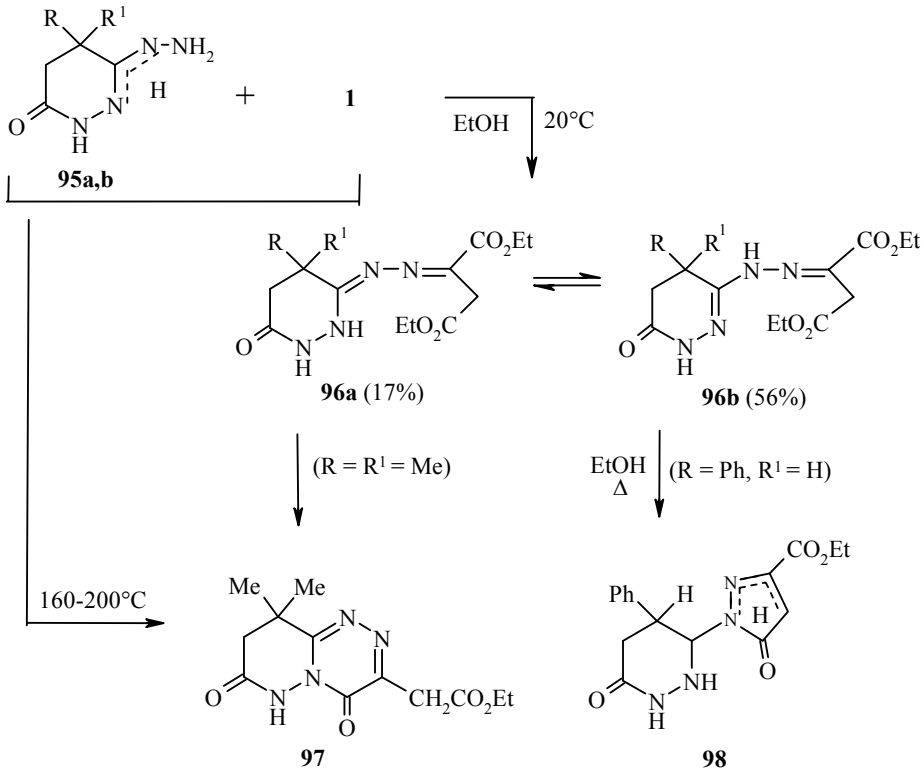


92

93a,b **94a,b**

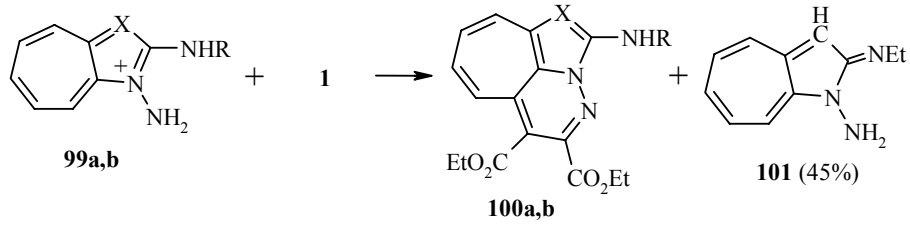
93, 94 a R = R^1 = H (73%); **b** R = NO_2, R^1 = $NHNH_2$ (65%)

Derivatives of 3-hydrazinotetrahydropyridazine-3,6-dione (**95**) react readily with oxaloacetic ester with the formation of bis(ethoxycarbonyl)alkylidene derivatives **96** [42]. The condensation product can exist both in the enamine form **96a** and in the imine form **96b**, and further cyclization by boiling in alcohol leads to the formation of compounds **97** and **98**.



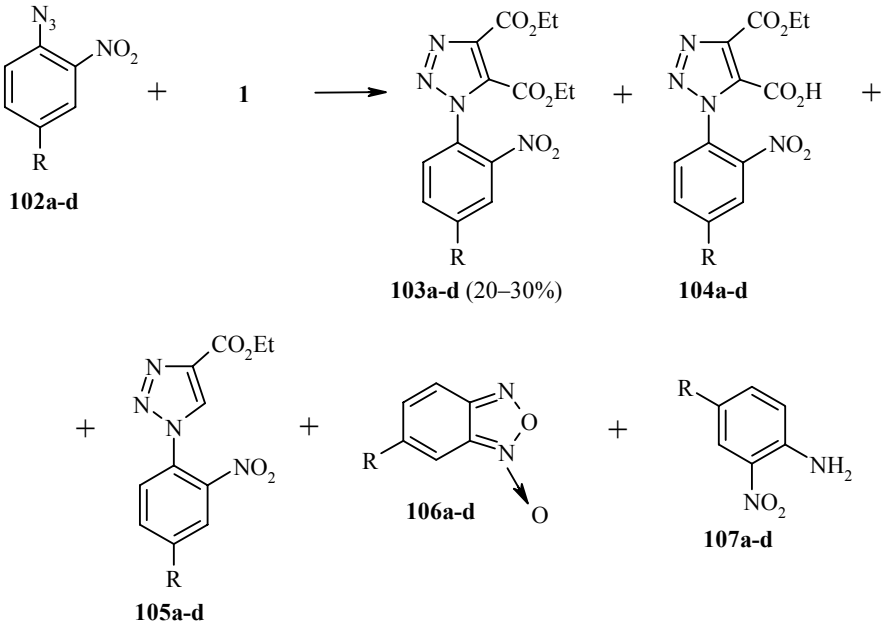
95a,b **96a** (17%) **96b** (56%) **97** **98**

For cyclic hydrazonium salts **99a**,**b** in reaction with oxaloacetic ester cyclocondensation takes place at position 8 with the formation of derivatives of benzazulenes **100a**,**b**. In the case of compound **99b** the process is accompanied by deprotonation, leading to compound **101** [43].



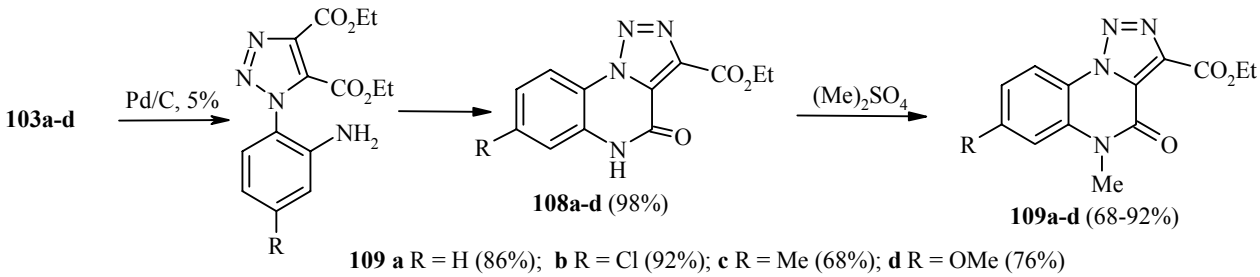
99, 100 a R = H, X = N (25%); **b** R = Et, X = CH (30%)

In reaction with aromatic azides the dicarbon fragment of oxaloacetic ester participates in the formation of a triazole ring. Thus, reaction with 2-nitrophenyl azides **102a-d** by heating at 55°C in alcohol for several hours gives a mixture of diethyl 1-(2-nitrophenyl)-1,2,3-triazole-4,5-dicarboxylates **103a-d** (20-30%), 5-carboxy-4-ethoxycarbonyl-1,2,3-triazoles **104a-d**, and their decarboxylation products (4-ethoxycarbonyl-1,2,3-triazoles **105a-d**), and also benzoxadiazole N-oxides **106a-d** and anilines **107a-d**, which can be separated by chromatography [44].



a R = H, **b** R = Cl, **c** R = Me, **d** R = OMe

The nitrophenyltriazoles **103a-d** find other applications in synthesis. Thus, after reduction of the nitro group and subsequent intramolecular cyclization derivatives of triazoloquinoxalines **108a-d** are formed, and they react readily with dimethyl sulfate, forming the N-methyl derivatives **109a-d**.



109 a R = H (86%); **b** R = Cl (92%); **c** R = Me (68%); **d** R = OMe (76%)

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