Chemistry of Heterocyclic Compounds, Vol. 46, No. 6, 2010

PYRROLO[1,2-*a*]QUINOXALINES BASED ON QUINOXALINES (REVIEW)

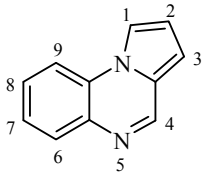
V. A. Mamedov[1]* and A. A. Kalinin[1]

Published data on methods for the synthesis of pyrrolo[1,2-a]quinoxalines, based on derivatives of quinoxalines and also on compounds that are not initially derivatives of quinoxalines or pyrroles are summarized and classified.

Keywords: pyrrolo[1,2-*a*]quinoxalines, quinoxalines.

Derivatives of pyrrolo[1,2-*a*]quinoxalines have valuable characteristics and, in particular, marked biological activity and are a subject of constant interest. In spite of this, however, data on the synthesis of these compounds remain disconnected. The only review [1], devoted to pyrroloquinoxalines and appearing in a monograph published in 1979, presents data mostly covering the period from 1965 to 1975. The review is devoted not only to the synthesis of pyrrolo[1,2-*a*]quinoxalines but also to the synthesis of pyrrolo[2,3-*b*]-, pyrrolo[3,4-*b*]-, and pyrrolo[1,2,3-*de*]quinoxalines and their physicochemical characteristics. While covering so many questions in a single review the authors simply present the existing information without analyzing the methods used for their synthesis. From the review it is difficult to form an opinion as to which of the methods is more promising and to think of any new methods for their synthesis.

In the present review an attempt is made to examine all possible ways of assembling the pyrrolo-[1,2-*a*]quinoxaline skeleton from various fragments on the basis of an analysis of its structure.



Pyrrolo[1,2-*a*]quinoxalines

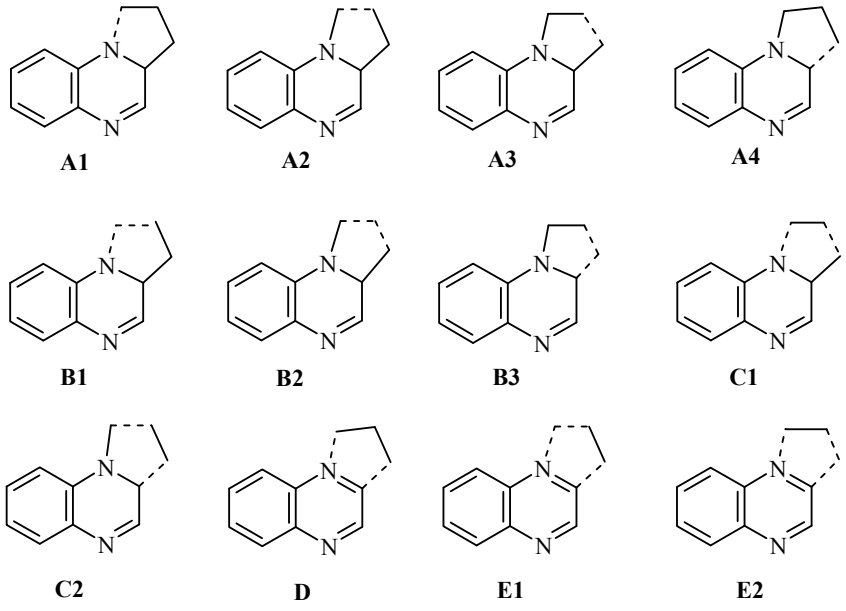
Without touching on the integrity of the benzene ring, the creation of the pyrrolo[1,2-*a*]pyrazine system can be represented by one of five types of construction depending on the number of atoms entering into the composition of the initial fragments: **A** (9+0), **B** (8+1), **C** (7+2), **D** (6+3), **E** (6+2+1 or 6+1+2); the number of

* To whom correspondence should be addressed, e-mail: mamedov@iopc.kcn.ru.

[1]Institution of the Russian Academy of Sciences, A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center of the Russian Academy of Sciences, Kazan 420088, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 803-831, June, 2010. Original article submitted August 19, 2009.

atoms in each of the fragments is given in parentheses. In other words, the synthetic equivalents that correspond to the principles of construction of heterocycles of type **A** must consist of a fragment capable of undergoing intramolecular cyclocondensation. Each of the next three types (**B-D**) of construction of the tricyclic system requires two reagents corresponding to two synthetic equivalents: in the case of **B** one- and eight-atom; in the case of **C** two- and seven-atom; in the case of **D** three- and six-atom. Case **E** requires three reagents corresponding to three synthetic equivalents: six-, two-, and one-atom or six-, one-, and two-atom. Such an approach will make it possible to correlate the theoretically possible schemes of assembly to real syntheses, while taking account of the nature of the reaction centers. This makes it possible not only to rationalize already known methods of synthesis but also to determine which of the methods of assembly have not yet been used and why and to attempt to "think up" new reactions by means of which the pyrrolo[1,2-*a*]quinazoline system could be constructed.

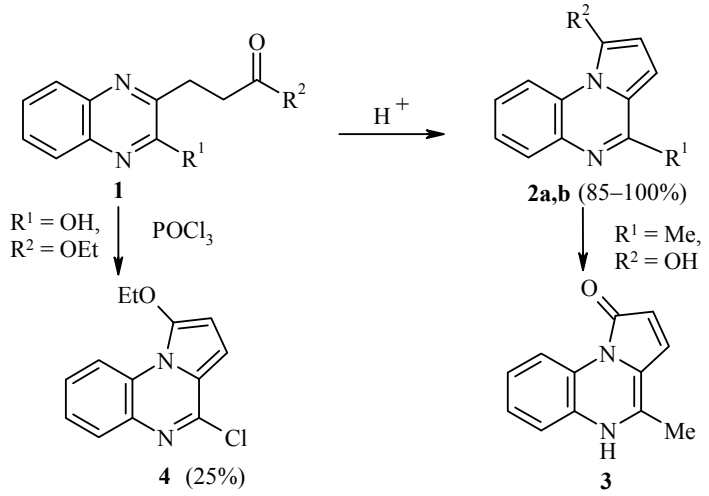


Possible variants of the construction of the pyrrolo[1,2-*a*]quinazoline system on the basis of quinoxalines

All known methods for the synthesis of the pyrrolo[1,2-*a*]quinoxaline system can be divided into three groups. The first group of methods is based on derivatives of quinoxaline, the second group contains methods based on pyrroles, and the third group contains other methods including the recyclization of other heterocycles and also syntheses from non-heterocyclic systems. This review examines methods of synthesis based on derivatives of quinoxaline and the methods of the third group. Possible variants of the construction of the pyrrolo[1,2-*a*]quinoxaline system based on quinoxalines are presented below.

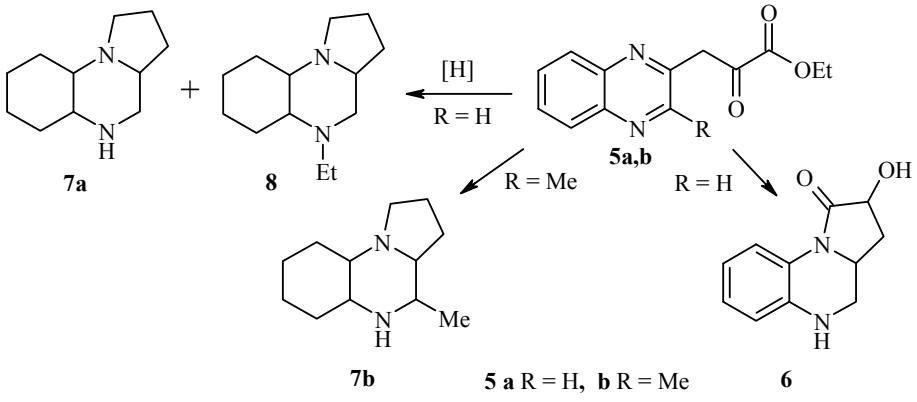
Production Methods of Type A (Version A1)

One of the most widespread and most widely used among methods for the synthesis of pyrrolo-[1,2-*a*]quinoxalines is the method involving the intramolecular cyclization of derivatives of quinoxaline with substituents at position 2 and containing at least three carbon atoms with reaction centers capable of nucleophilic attack. Quinoxalines **1**, containing a γ-carbonylalkyl substituent at position 2 (ketones, carboxylic acids, esters) undergo intramolecular cyclization under the influence of acids with the formation of pyrroloquinoxalines **2-4** [2-5].

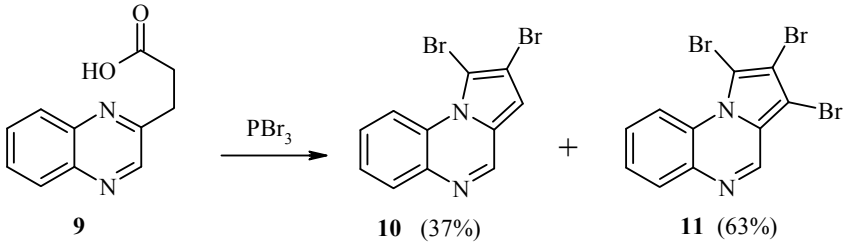


2 a $R^1 = R^2 = H$, **b** $R^1 = Me$, $R^2 = H$

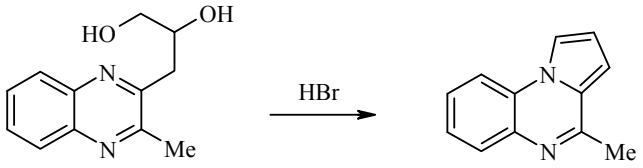
Reduction of the quinoxalines **5** leads to hydropyrroloquinoxalines **6-8** [6, 7]. The pyrrolo-[1,2-*a*]quinoxaline system (compound **6**) was first obtained by this method [7]. During the reductive cyclization of ethyl quinoxalin-2-yl- and 3-methylquinoxalin-2-ylpyruvates **5** in the presence of copper chromite at high temperature, the perhydropyrrolo[1,2-*a*]quinoxalines **7** and **8** are formed.



During closure of the pyrrole ring as a result of the treatment of compound **9** with PBr_3, a mixture of dibromo- and tribromopyrroloquinoxalines **10** and **11** is formed [8].

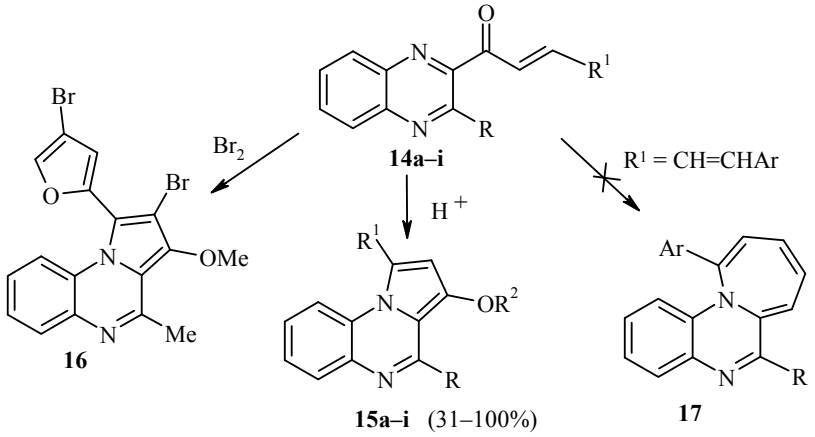


During the action of HBr, 2,3-dihydroxypropyl-4-methylquinoxaline (**12**) undergoes intramolecular cyclization with the formation of 4-methylpyrrolo[1,2-*a*]quinoxaline (**13**) [9].



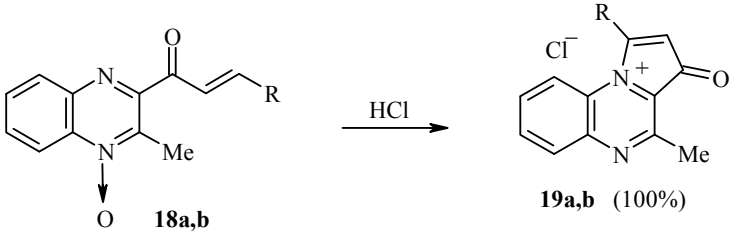
12 **13** (67%)

When treated with concentrated hydrochloric acid in methanol, the 2-(2-ylidene)acetylquinoxalines **14a-i**, easily obtained from the corresponding 2-acetylquinoxalines and aryl(hetaryl)aldehydes, form 1-substituted derivatives of pyrrolo[1,2-*a*]quinoxalines **15a-i**. Intramolecular closure also occurs successfully in solution in CCl_4 in the presence of molecular bromine, but here the dibromide **16** is formed [10, 11]. The use of compounds **14a**,**i** [12], which have competing reaction centers capable of undergoing nucleophilic attack, in this reaction leads not to the supposed derivatives of azepino[1,2-*a*]quinoxaline but to the formation of the pyrrolo[1,2-*a*]quinoxalines **15h**,**i**.



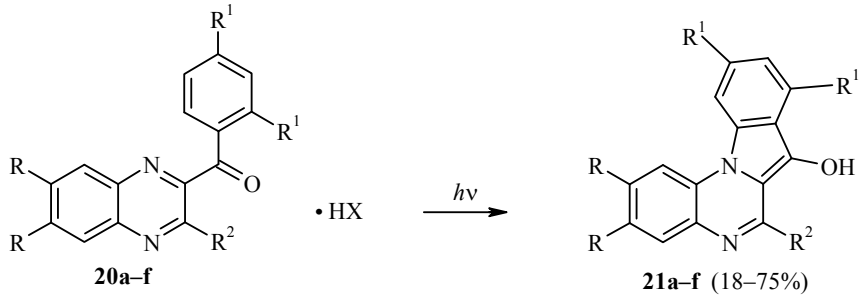
14, **15 a** R = R^2 = H, R^1 = furyl-2, **b**–**g** R = Me, **b** R^1 = furyl-2, R^2 = H, **c** R^1 = Ph, R^2 = Me, **d** R^1 = Ph, R^2 = Ac, **e** R^1 = C_6H_4OMe-*p*, R^2 = Me, **f**–**i** R^2 = H, **f** R^1 = $C_6H_4NO_2$-*p*, **g** R^1 = CH=CHPh, **h** R = H, R^1 = CH=CHPh, **i** R = Me, R^1 = $CH=CHC_6H_4NO_2$

When ethanol solutions of 2-cinnamoyl-3-methylquinoxaline 4-oxide (**18a**) and 3-methyl-4-oxido-2-quin-oxalinyl 5-phenylpenta-2,4-dienyl ketone (**18b**) are boiled in the presence of hydrochloric acid the respective 4-methyl-3-oxo-1-phenyl- and 4-methyl-3-oxo-1-(2-phenylethenyl)-3H-pyrrolo[1,2-*a*]quinoxalin-10-ium chlorides **19a**,**b** are formed similarly with quantitative yields [13].



18, 19 a R = Ph, **b** R = CH=CHPh

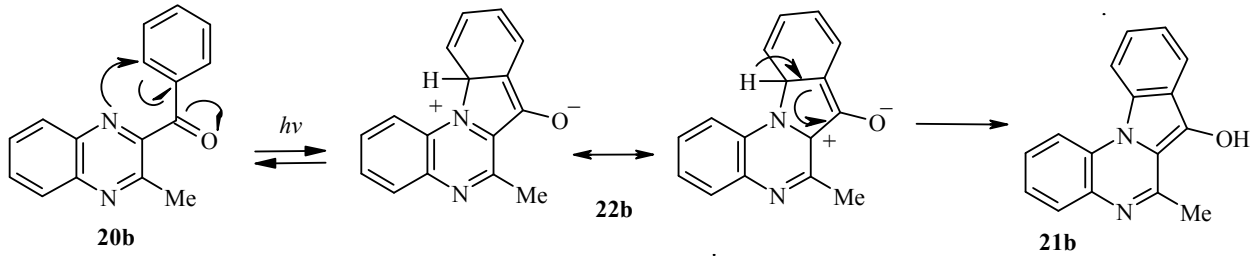
The double bond of the ethenoyl function can enter the aromatic system. Thus, substituted derivatives of benzoylquinoxaline **20a-f** undergo cyclization during UV irradiation; the cyclization is accelerated by the presence of trifluoroacetic or *p*-toluenesulfonic acid [14].



20a–f • HX $h\nu$ **21a–f** (18–75%)

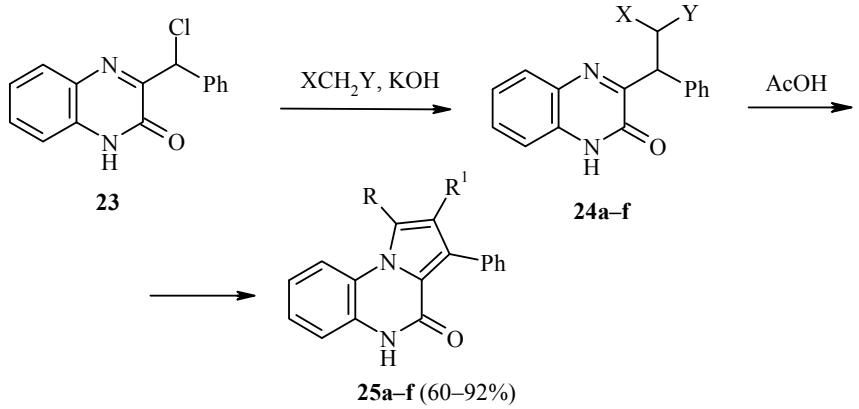
20 a X = CF_3COO, **b** HX is absent, **c–f** X = 4-$MeC_6H_4SO_3$; **20**, **21 a** R = R^1 = R^2 = H, **b** R = R^1 = H, R^2 = Me, **d** R = R^1 = H, R^2 = Bn, **e** R = H, R^1 = R^2 = Me, **f** R = Me, R^1 = H, R^2 = Me

The proposed mechanism of photocyclization for the transformation **20b** → **21b** and the role of protonation are clear from the scheme [14].



20b *hv* **22b** **21b**

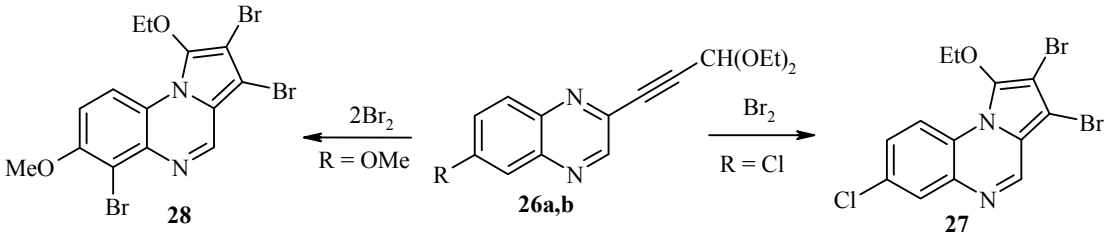
The quinoxalines **24** with β-dicarbonyl, β-dinitrile, and β-nitrilecarbonyl fragments, produced in the reaction of 3-(α-chlorobenzyl)quinoxalin-2-one (**23**) with the anions of β-dicarbonyl compounds, dicyanomethane, and cyanoacetic ester, form the pyrroloquinoxalines **25** when treated with acetic acid [15]. This cyclization could lead to one and/or two compounds differing in the position of the substituents R^1 and R^2, but only the tricyclic compounds **25a-f** are formed as a result of the reaction.



23 XCH_2Y, KOH **24a–f** AcOH **25a–f** (60–92%)

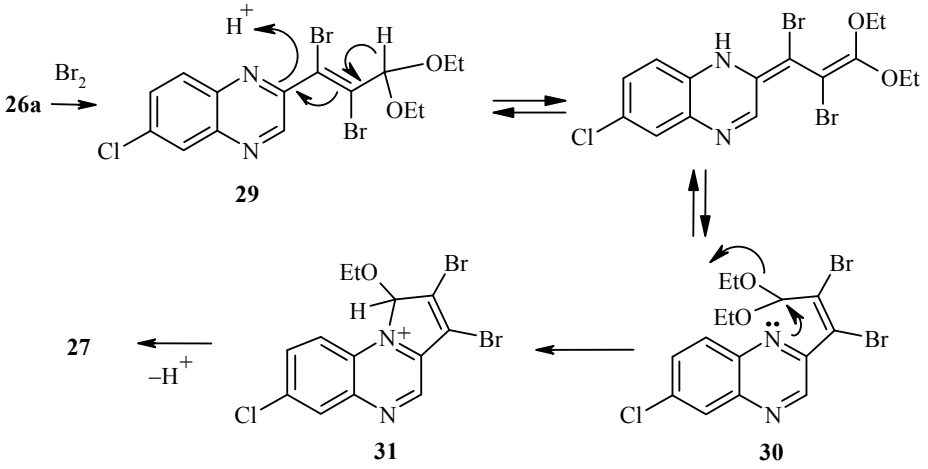
24 a X = Y = Ac, **b** X = Ac, Y = Bz, **c** X = Y = Bz , **d** X = Y = CN, **e** X = Ac, Y = COOEt; **f** X = CN, Y = COOEt; **25 a** R = Me, R^1 = Ac, **b** R = Me, R^1 = Bz, **c** R = Ph, R^1 = Bz, **d** R = NH_2, R^1 = CN, **e** R = OEt, R^1 = Ac, **f** R = OEt, R^1 = $CONH_2$

6-Chloro-2-(3,3-diethoxypropyn-1-yl)quinoxaline (**26a**), obtained by the cross-coupling of 2,6-dichloroquinoxaline and 3,3-diethoxypropyne, forms the pyrroloquinoxaline **27** when treated with molecular bromine. If the 6-methoxy derivative of quinoxaline **26b** is used in this reaction, position 5 of the initial quinoxaline ring undergoes bromination on account of the strong electron-donating effect of the methoxyl group, and this leads to the tribromo derivative of pyrrolo[1,2-*a*]quinoxaline **28**.

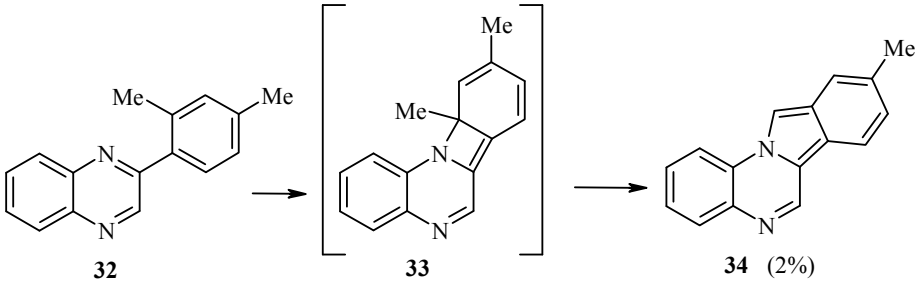


26 a R = Cl, **b** R = OMe

The pyrroloquinoxaline **27** is formed through a stage involving initial *trans* addition of bromine at the triple bond (the formation of compound **29**) followed by prototropic isomerization to the *cis* isomer **30**, which undergoes cyclization to the pyrroloquinoxaline with the elimination of alcohol [16].

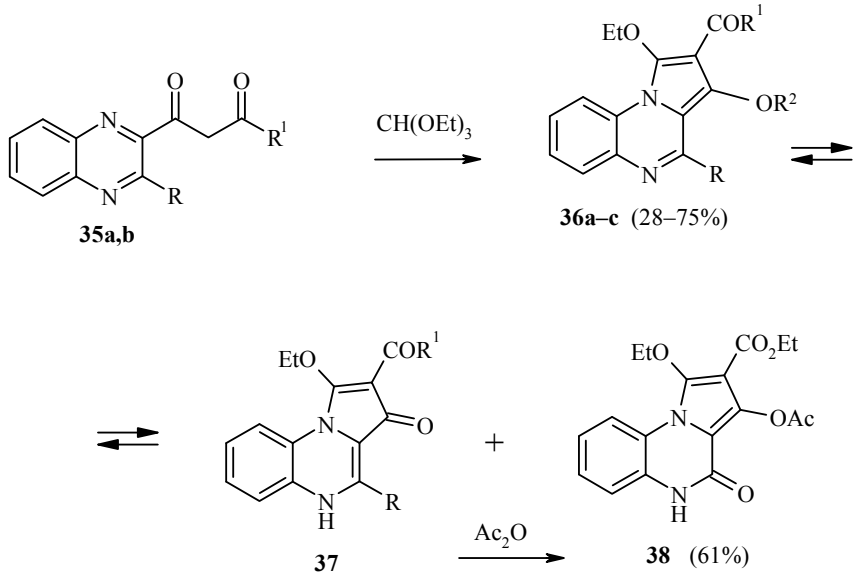


An essential condition for the closure of the pyrrole ring according to type **A** in 2-substituted quinoxalines is the presence of a three-carbon fragment, and it is not necessary here that the γ-carbon atom of this fragment initially contained a suitable reaction center. In certain cases the reaction centers can arise under the reaction conditions. For example, the pyrolysis of 2-(2,4-dimethylphenyl)quinoxaline (**32**) at 550-560°C in the presence of the industrial dehydrogenation catalyst K-16 [17] leads to 9-methylisoindolo[2,1-*a*]quinoxaline (**34**) [18].



Production Methods of Type B (Version B1)

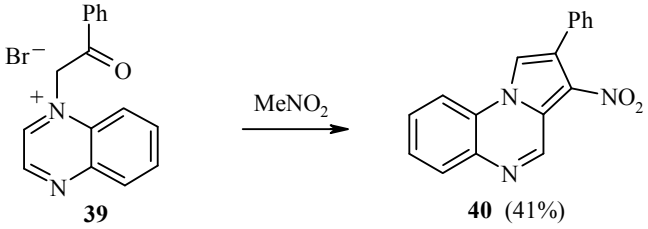
During the condensation of ethyl (3-chloro-2-quinoxaloyl)acetate (**35a**) with orthoformic ester in the presence of Ac_2O (65-70°C) the formation of two substances was observed: the main chlorine-containing reaction product **36a** and a minor chlorine-free compound **38**. The amount of compound **38** increased with increase in temperature, and at 100-105°C it became the main reaction product. It was also shown that compound **36b** can be obtained by heating the initial compound **35a** with orthoformic ester at a higher temperature (100-105°C). The chain **35** → **36** → **38** was therefore investigated [19, 20]. The condensation of the quinoxaline **35b** with orthoformic ester at a higher temperature (up to 160°C) leads exclusively to the pyrroloquinoxaline **36c**.



35 a R =Cl, R^1 = OEt, **b** R = OEt, R^1 = Me; **36 a** R =Cl, R^1 = OEt, R^2 = Ac,
b R = Cl, R^1 = OEt, R^2 = H, **c** R = OEt, R^1 = Me, R^2 = H

Production Methods of Type B (Version B3)

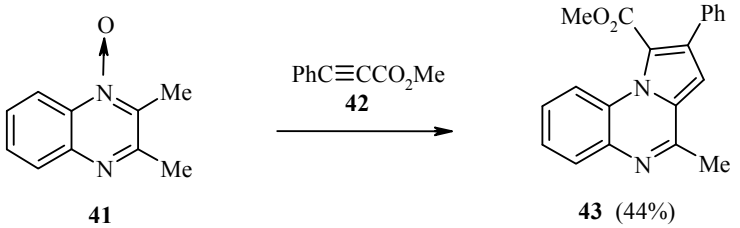
The reaction of 1-phenacylquinoxalinium bromide (**39**) with nitromethane in its boiling solution in the presence of Na_2CO_3 for 6 h leads to 3-nitro-2-phenylpyrrolo[1,2-*a*]quinoxaline (**40**) [21].



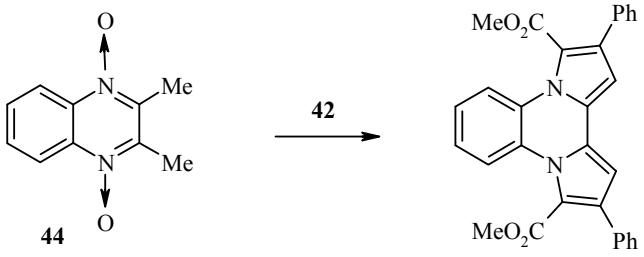
Production Methods of Type C (Version C1)

Cycloaddition Reactions

As a rule, in these reactions the quinoxaline derivative directly or indirectly fulfills the function of a 1,3-dipolar compound, and this determines the path to the formation of the final product – pyrrolo[1,2-*a*]quinoxaline – and its structure almost irrespective of the nature of the 1,3-dipolarophile. During the reaction of 2,3-dimethylquinoxaline monooxide (**41**) and 2,3-dimethylquinoxaline dioxide (**44**) with methyl phenylpropargylate (**42**) in molar ratios of 1:1 and 1:2 respectively compounds **43** and **45** are formed [22].

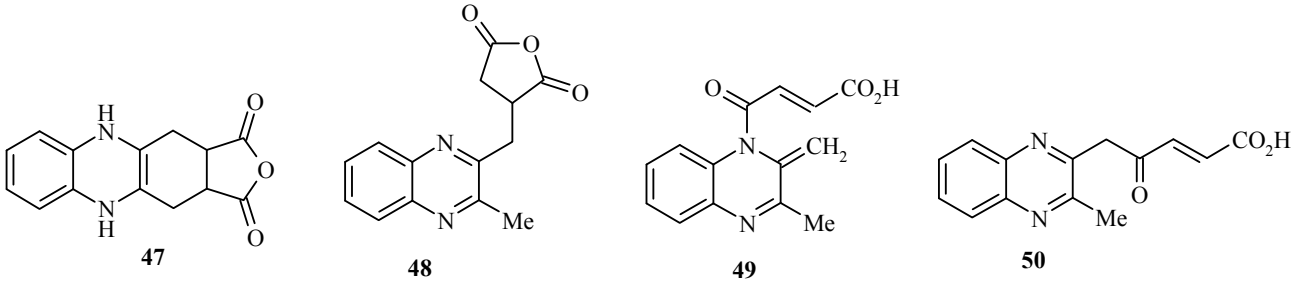


41 **43** (44%)



44 **45** (20–35%)

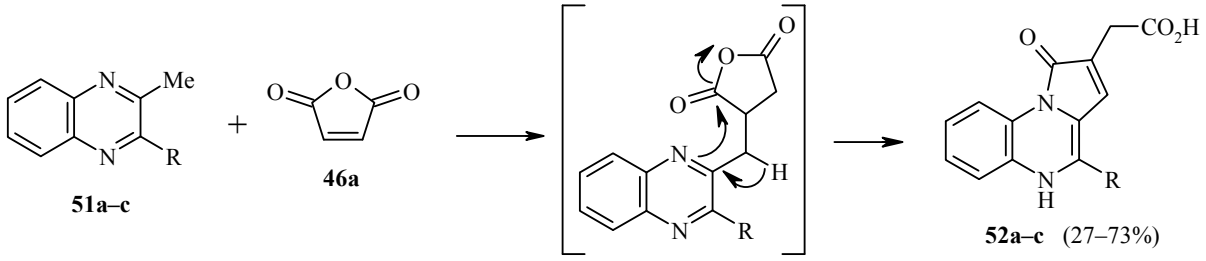
It is well known that maleic anhydride (**46a**) is capable of undergoing three types of reaction: Condensation with dienes with the participation of the double bond and the formation of a Diels–Alder adduct; Addition at the double bond with the formation of a derivative of succinic anhydride; Reaction of one of the carbonyl groups followed by opening of the anhydride system [23, 24]. Compounds **47**-**50** could be formed in the reaction of maleic anhydride with 2,3-dimethylquinoxaline **51a**.



47 **48** **49** **50**

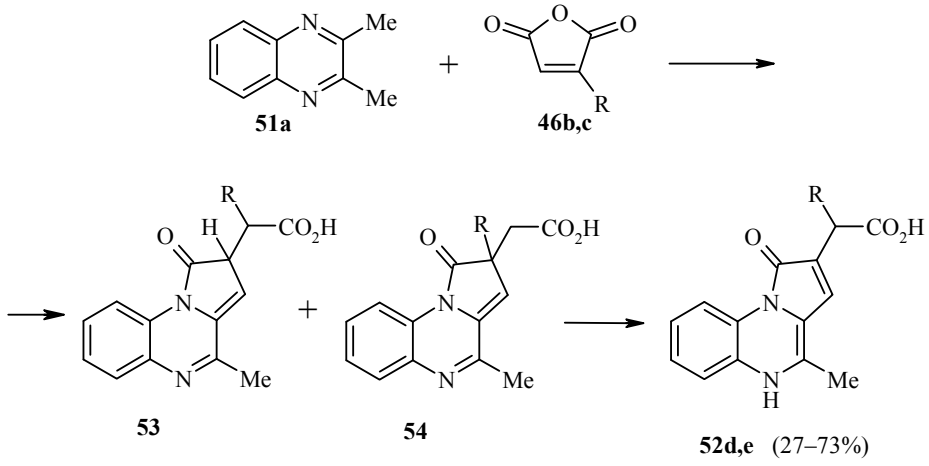
However, the reaction of 2,3-dimethylquinoxaline **51a** with maleic anhydride (**46a**) under standard conditions [4] takes place with the empirical formula $C_{14}H_{12}N_2O_3$, the IR spectrum of which does not contain bands for the stretching vibrations of the anhydride groups but there are bands for the stretching vibrations characteristic of NH, the OH of the carboxyl function, the double bond, and

an amide vinylog. The NMR spectra and the chemical properties of the "adduct" show that pyrrolo[1,2-*a*]quinoxaline **52a** is formed as a result of the reaction, and this can be represented by the scheme below [4, 5]. Accordingly, the condensation of maleic anhydride with 2-methylquinoxaline and 2-methyl-3-phenylquinoxaline gives 2-carboxymethyl- (**52b**) and 2-carboxymethyl-4-phenyl-pyrrolo[1,2-*a*] quinoxalin-1(5H)-ones (**52c**) [4, 25].



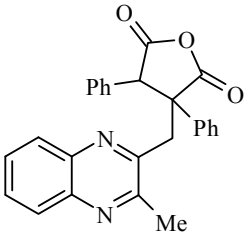
51, 52 a R = Me, **b** R = H, **c** R = Ph

In the case of monosubstituted derivatives of maleic anhydride the two possible isomeric succinic anhydrides are formed; as a result of opening and closure of the ring, like the unsubstituted derivatives, they give 1-oxo-1,2-dihydropyrrolo[1,2-*a*]quinoxalines **53** and **54**, and here only the first of them isomerize to the 1-oxo-1,5-dihydropyrrolo[1,2-*a*] quinoxalines **52d**,**e** [9].



46b, **52d** R = Me; **46c**, **52e** R = Ph

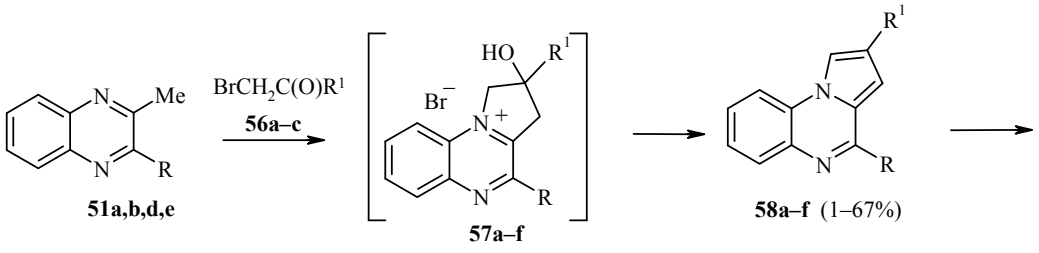
If disubstituted maleic anhydride is used in this reaction, even with boiling in toluene solution for 46 h, the process does not go past the stage of formation of the corresponding derivative of succinic acid **55**, which is isolated with a yield of 90% [9].

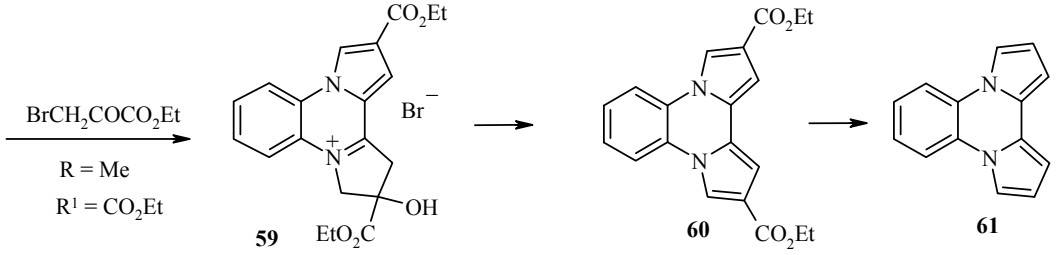


55

The authors of [5] cast some doubt on all the previous investigations [23, 24] concerning study of the reaction of 2,3-dimethylquinoxaline with maleic anhydride, the products of which were erroneously assigned one of the above-mentioned structures **47-50**, and showed that pyrrolo[1,2-*a*]quinoxaline is formed as a result of this reaction.

The second general method for the synthesis of pyrrolo[1,2-*a*]quinoxalines according to the **C1** version involves the reaction of mono- and dimethylquinoxalines with α-halo ketones [9, 26-30]. The tricyclic system in this case is produced after treatment of the intermediately formed quaternary salts **57a-f** with sodium alcoholate. The effectiveness of the reaction depends on how successfully the quaternary salt is formed, and this in turn is determined by the nucleophilicity of the nitrogen atom of the quinoxaline system at which the reaction occurs and by the nature of the alkylating reagent. For example, the reaction of the ethyl bromopyruvate (**56a**) with 2,3-dimethylquinoxaline (**51a**) [26] gives 67% of the tricyclic compound **58d**, while the reaction of 2-chloro-3-methylquinoxaline (**51d**) [27] with ethyl bromopyruvate (**56a**) takes place with a yield of only 26% of the pyrrolo[1,2-*a*]quinoxaline derivative **58b**. At the same time only 14% of the required substance **58e** is formed in the reaction of 2,3-dimethylquinoxaline **51a** with phenacyl bromide (**56b**) [9], and only 1% of the pyrroloquinoxaline **58f** is formed with bromoacetone (**56c**).

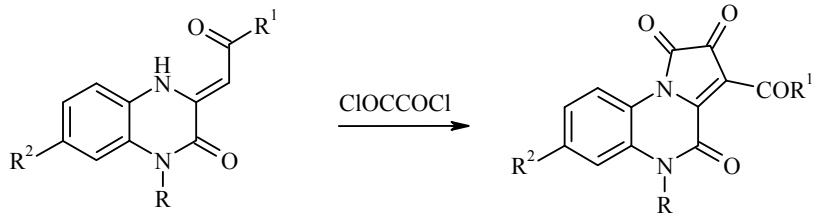




51 a R = Me, **b** R =H, **d** R = Cl, **e** R = NMe_2; **56 a** R^1 = CO_2Et, **b** R^1 = Ph, **c** R^1 = Me;
57, **58 a–d** R^1 = CO_2Et, **a** R =H, **b** R = OH, **c** R = NMe_2, **d** R = Me, **e** R = Me, R^1 = Ph,
f R = R^1 = Me

The presence of a methyl substituent at position 4 of compound **58d** made it possible, with identical strategy, to synthesize with a 56% yield 2,11-di(ethoxycarbonyl)dipyrrolo[1,2-*a*;2',1'-*c*]quinoxaline (**60**), which was converted into unsubstituted dipyrrolo[1,2-*a*;2',1'-*c*]quinoxaline **61** according to the scheme presented above [26].

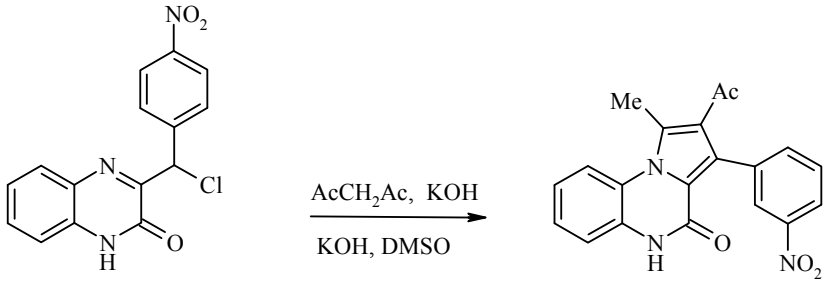
In a number of cases the reaction of the quinoxalines **62a-s** with oxalyl chloride with boiling in anhydrous chloroform at 60-63°C for 2-2.5 h leads to the formation of 3-aroyl- and heteroyl-1,2,4,5-tetra-hydropyrrolo[1,2-*a*]quinoxaline-1,2,4-triones **63** with almost quantitative yields [31-34].



62 a–s **63a–s** (59–98%)

62, 63 a–g R = R^2 = H, **a** R^1 = Ph, **b** R^1 = 4-MeC_6H_4, **c** R^1 = 4-$MeOC_6H_4$, **d** R^1=4-$NO_2C_6H_4$, **e** R^1 = 2-furyl, **f** R^1 = 2-thienyl, **g** R^1= 1,3-thiazol-5-yl; **62, 63 h–r** R= Ph, R^2 = H, **h** R^1 = H, **i** R^1 = 4-MeC_6H_4Me, **j** R^1 = 4-$MeOC_6H_4$, **k** R^1 = 4-$EtOC_6H_4$, **l** R^1 = 4-FC_6H_4, **m** R^1 = 4-ClC_6H_4, **n** R^1 = 4-BrC_6H_4, **o** R^1 = 4-$NO_2C_6H_4$, **p** R^1 = 2-furyl, **q** R^1 = 5-methyl-2-furyl, **r** R^1 = 5-chloro-2-thienyl; **s** R= H, R^1 = Ph, R^2 = NO_2

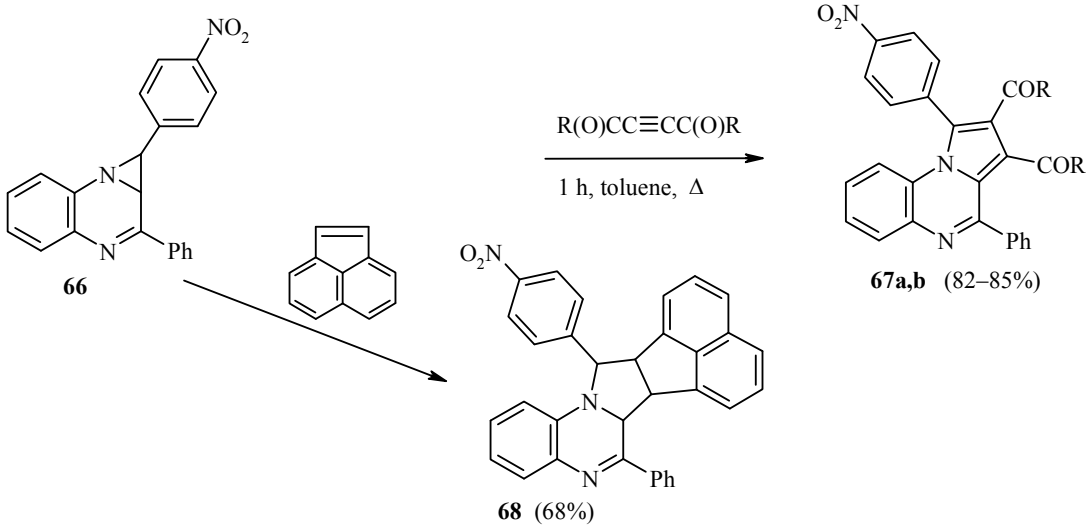
The reaction of 3-[α-chloro(*p*-nitrobenzyl)]quinoxalin-2-one (**64**) with acetylacetone in the presence of KOH without isolation of the corresponding C-alkylation product leads to the formation of the pyrroloquinoxaline **65** [15].



64 **65** (60%)

Production Methods of Type C (Version C2)

1-(*p*-Nitrophenyl)-2-phenyl-1,1*a*-dihydroazirino[1,2-*a*]quinoxaline (**66**), readily obtainable by the reaction of 2,3-dibromo-3-(*p*-nitrophenyl)-1-phenyl-1-propanone with *o*-phenylenediamine, reacts with 1,3-dipolarophiles – dimethyl acetylenedicarboxylate, dibenzoylacetylene, and acenaphthylene – in boiling

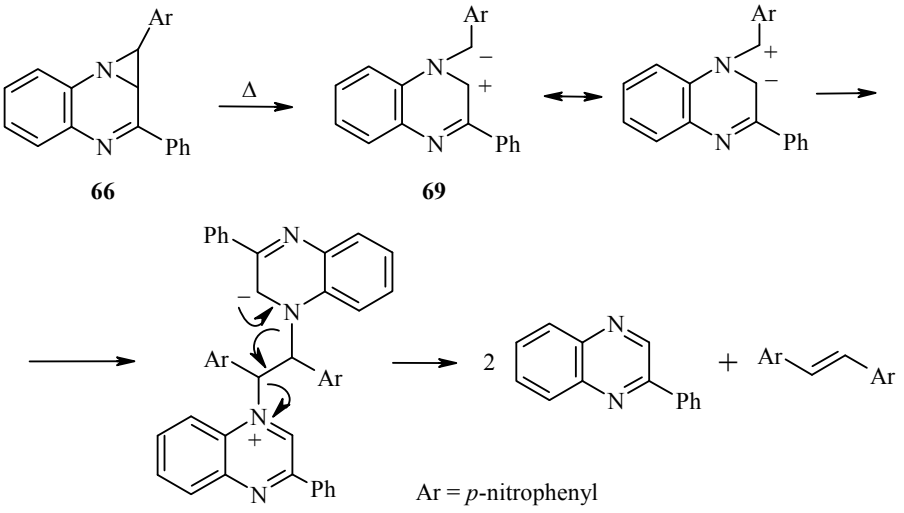


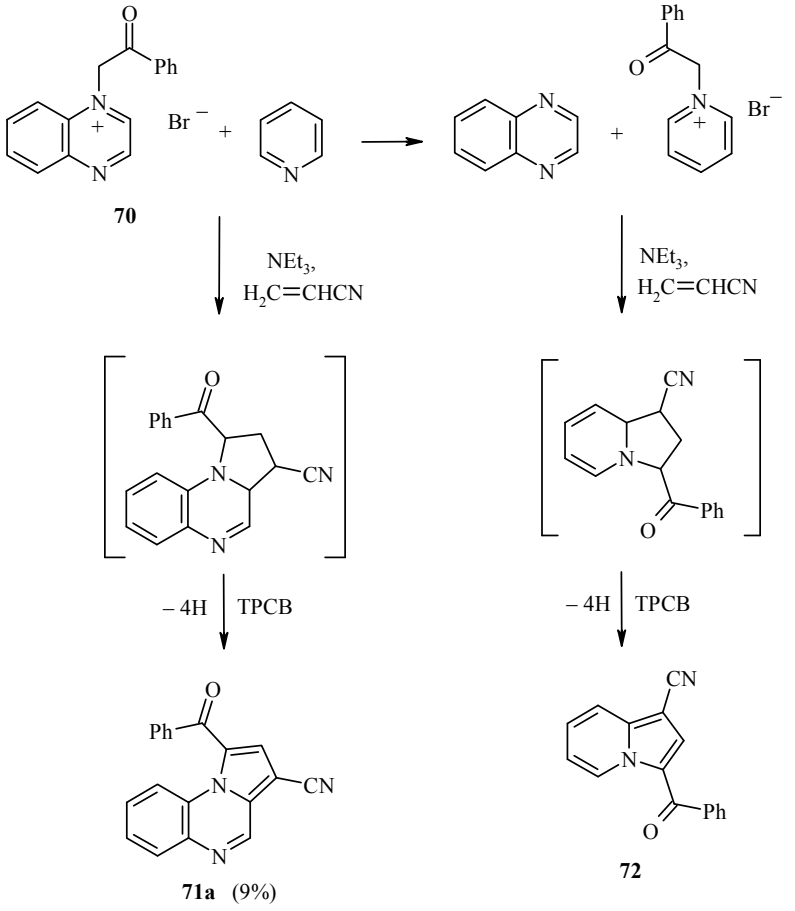
66 **67a,b** (82–85%) **68** (68%)

67 a R = OMe, **b** R = Ph

toluene with the formation of derivatives of 1-*p*-nitrophenyl-4-phenylpyrrolo[1,2-*a*]quinoxaline **67** in the first two cases and 13-*p*-nitrophenyl-6-phenyl-6*a*,6*b*,12*b*,13-tetrahydroacenaphtho[1',2':3,4]pyrrolo[1,2-*a*]quinoxaline (**68**) in the third [35].

The fact that these reactions take place through the 1,3-dipolar intermediate **69**, arising as a result of thermal cleavage of the C–C bond of the azirino[1,2-*a*]quinoxaline system, is favored by the formation of *p*,*p'*-dinitrostilbene and 2-phenylquinoxaline [35] according to the following scheme.

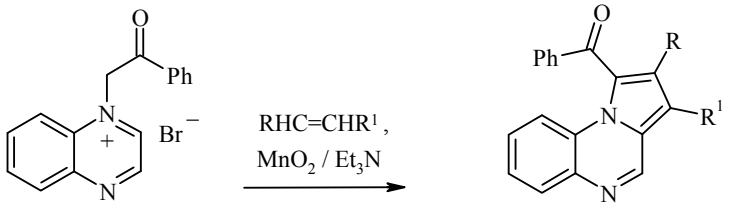




TPCB = tetrakis(pyridine)cobalt(II) bichromate

To realize the strategy for the synthesis of pyrrolo[1,2-*a*]quinoxalines denoted by the symbol **C2** it could be possible to use the 1,3-dipolar cycloaddition of the quinoxalinium N-ylide, produced *in situ* by the reaction of 1-phenacylquinoxalium bromide with triethylamine, with various 1,3-dipolarophiles if the formation of the 1-phenacylquinoxalinium bromide proceeded well and without side processes. Unfortunately, 1-phenacylquinoxalinium bromide is formed with a yield of only 28% as a result of prolonged standing (one month) of the mixture of quinazoline and phenacyl bromide in chloroform solution [36]. Boiling of the reaction mixture for 3 h leads to resin formation. When heated without a solvent for 10 min the mixture of quinoxaline and phenacyl bromide polymerizes. Nevertheless the desired salt can be obtained with a 30% yield by fusion of the mixture of reagents at 60°C for 5 min. Heating of a mixture of 1-phenacyl bromide, acrylonitrile, triethylamine, and Py + $Co(HCrO_4)_2$ in DMF solution at 80-90°C for 5 h leads to the expected 1-benzoyl-3-cyanopyrrolo-[1,2-*a*]quinoxaline (**71a**) with a yield, unfortunately, of only 9%. The main reaction product (59%) is 3-benzoyl-1-cyanoindolizine (**72**) [37, 38]. The 1,3-dipolar cyclic adduct **72** obviously results from reaction of the acrylonitrile with the N-phenacylpyridinium bromide formed as a result of disproportionation of the salt **70** by pyridine (a stronger base than quinoxaline), which appears in the reaction mixture as a result of decomposition of the tetrakis(pyridine)cobalt(II) bichromate.

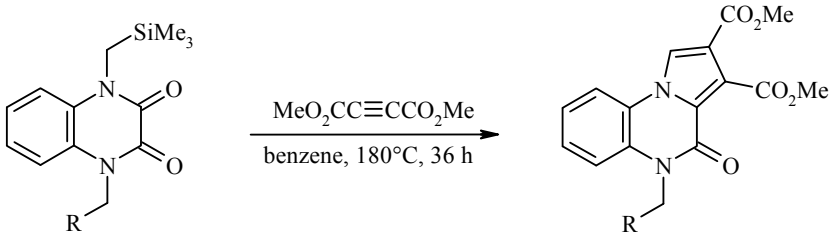
In order to avoid this effect an attempt was made to replace TPCB by the more readily accessible oxidizing agent MnO_2. Compound **71a** was formed with a yield of 48%. When the analogous procedure was used the pyrrolo[1,2-*a*]quinoxalines **71b-e** were obtained with moderate yields from methyl acrylate, methyl vinyl ketone, diethyl fumarate, and N-phenylmaleimide respectively [38].



70 **71a–e** (48–52%)

71 a–c R = H, **a** R^1 = CN, **b** R^1 = CO_2Me, **c** R^1 = COMe, **d** R = R^1 = CO_2Me, **e** R + R^1 = CO(NPh)CO

The quinoxalines **73** are converted by the action of acetylenedicarboxylic ester into the pyrroloquinoxalines **74** [39].

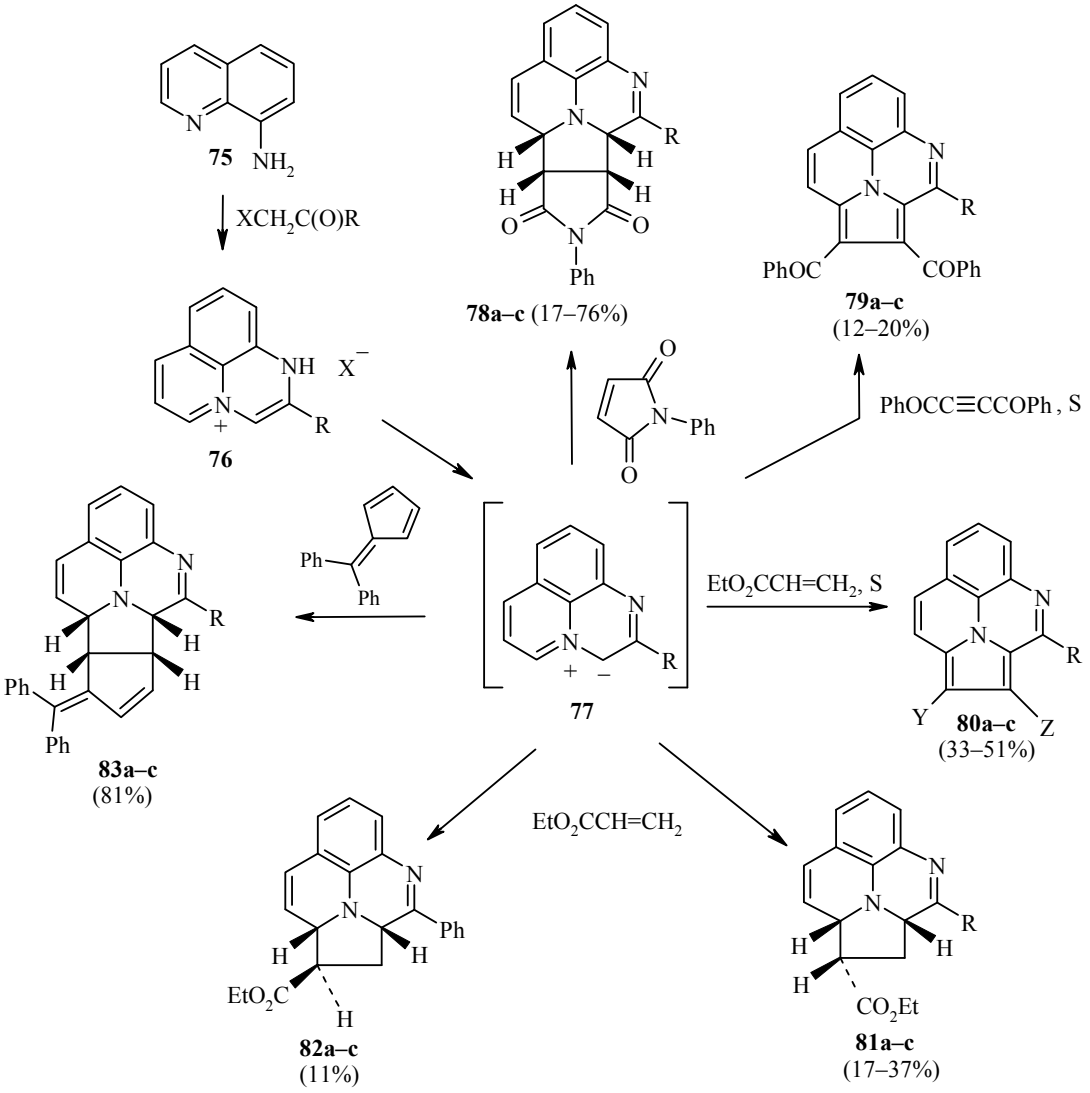


73a,b **74a,b** (68–100%)

73, 74 a R = H, **b** R = $SiMe_3$

Another synthetic equivalent of the type **C2** synthons in the construction of the pyrrolo[1,2-*a*]quinoxaline fragment entering in the condensed heterocyclic system can be the conjugated heterocyclic mesomeric betaines **77**, i.e., 2-substituted 1H-1,3aλ^5-diazaphenalen-3*a*-ium-3-ides produced *in situ* by the deprotonation of

2-substituted 1H-1,3aλ^5-diazaphenalen-3*a*-ium salts **76**, which are the products from condensation of 8-aminoquinoline (**75**) with α-halogeno ketones [40]. Since the betaines **77** cannot be isolated on account of their high reactivity, they were characterized in the form of the adducts **78-83**, which are derivatives of the pyrroloquinoxalines produced as a result of 1,3-dipolar addition of the betaines **77** to the various acetylenic and olefinic dipolarophiles.

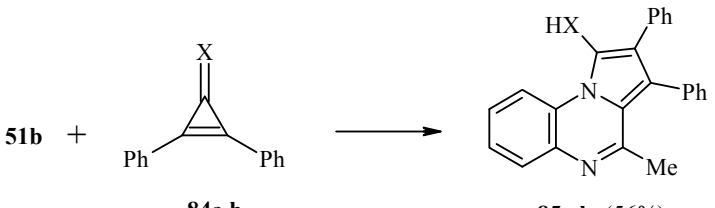


76–83 a R = Ph, X = Br, **b** R = Me, X = Cl, **c** R = H, X = Cl; **80** Y, Z = H, CO_2Et

Production Methods of Type D

Diphenylcyclopropane and diphenylcyclopropanethione, being synthetic equivalents of synthon **D**, react with various heterocyclic nitrogen compounds with annelation of the pyrrole ring; if the compound contains the –N=N– fragment, annelation as a rule involves both nitrogen atoms with the formation of a pyrazole-containing

condensed system. In these reactions, 2-methylquinoxaline (**51b**) acts as a synthetic equivalent of synthon **D** and, depending on the second reagent, is converted into the 1-hydroxy or 1-mercapto derivatives of pyrrolo-[1,2-*a*]quinoxaline **85** [41, 42].



84a,b **85a,b** (56%)

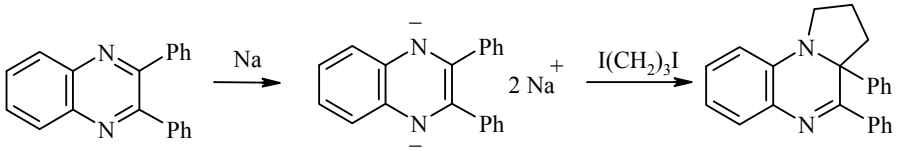
84, 85 a X = S, **b** X = O

However, a more recent investigation, involving study of the reaction of diphenylcyclopropenone with quinoxaline and 2-methylquinoxaline, showed that the 3-hydroxy derivative of pyrrolo[1,2-*a*]quinoxaline **86** [43] and not the 1-hydroxy derivative **85b**, as reported previously [41], is formed as a result of this reaction.

86a,b (58–60%)

86 a R = H, **b** R = Me

1,3-Diiodopropane can act as a more accessible synthetic equivalent of the three-carbon synthon in the construction of the pyrrolo[1,2-*a*]quinoxaline system by strategy **D**. By reaction with 1,3-diiodopropane in solution for 1 h the dianion of 2,3-diphenylquinoxaline (**88**), produced by the reaction of 2,3-diphenyl-quinoxaline (**87**) with two equivalents of metallic sodium, gives 3α,4-diphenyl-1,2,3,3α-tetrahydropyrrolo-[1,2-*a*]quinoxaline (**89**) [44].

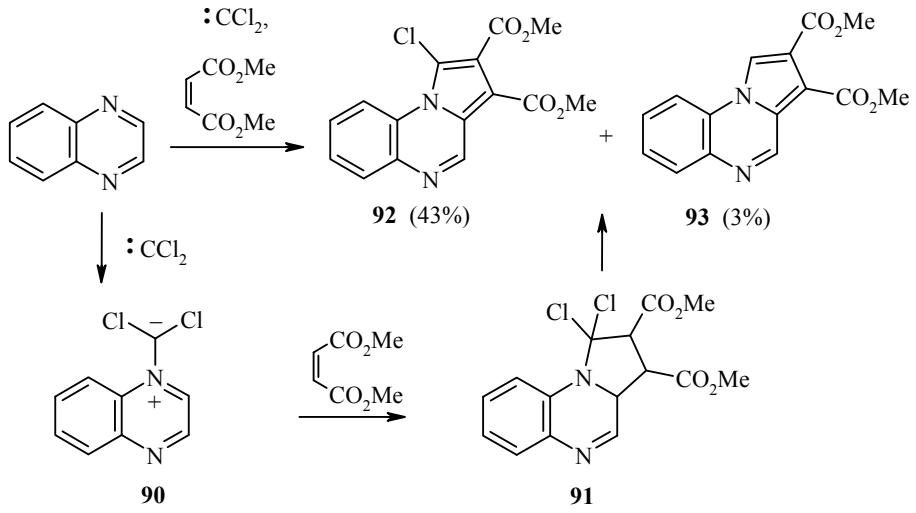


87 **88** **89** (27%)

Production Methods of Type E1

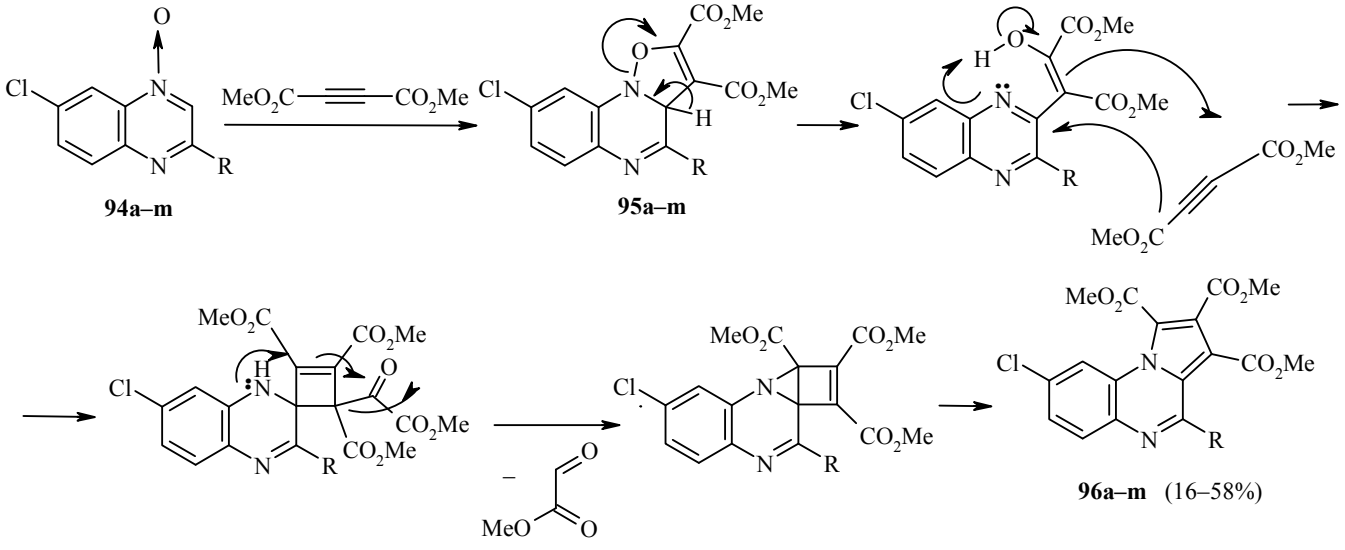
A more thorough retrosynthetic analysis of the structure of pyrrolo[1,2-*a*]quinoxalines demonstrates the possibility of synthesizing these compounds by a three-component reaction using reagents that can supply the one- and two-carbon fragments and also the quinoxaline system (symbol **E1**). The reaction of dichlorocarbene, generated from chloroform by the action of KOH, with quinoxaline in the presence of dimethyl maleate goes through the intermediate formation of an ylide – cycloammoniodichloromethanide **90**, the 1,3-dipolar cycloaddition of which to dipolarophiles gives the unstable derivatives of tetrahydropyrrolo[1,2-*a*]quinoxalines

91; they are dehydrogenated under the reaction conditions or by the action of an oxidizing agent to derivatives of pyrrolo[1,2-*a*]quinoxalines. In this case pyrrolo[1,2-*a*]quinoxaline **92** and trace quantities of its analog **93** not containing chlorine are formed [45].



Production Methods of Type E2

As a result of 1,3-dipolar addition to dimethyl acetylenedicarboxylate and methyl propargylate and depending on the molar ratio of the latter the quinoxaline N-oxides **94a-m** are transformed selectively into derivatives of isoxazolo[2,3-*a*]quinoxaline **95a-m** and pyrrolo[1,2-*a*]quinoxaline **96a-m** [46-51].



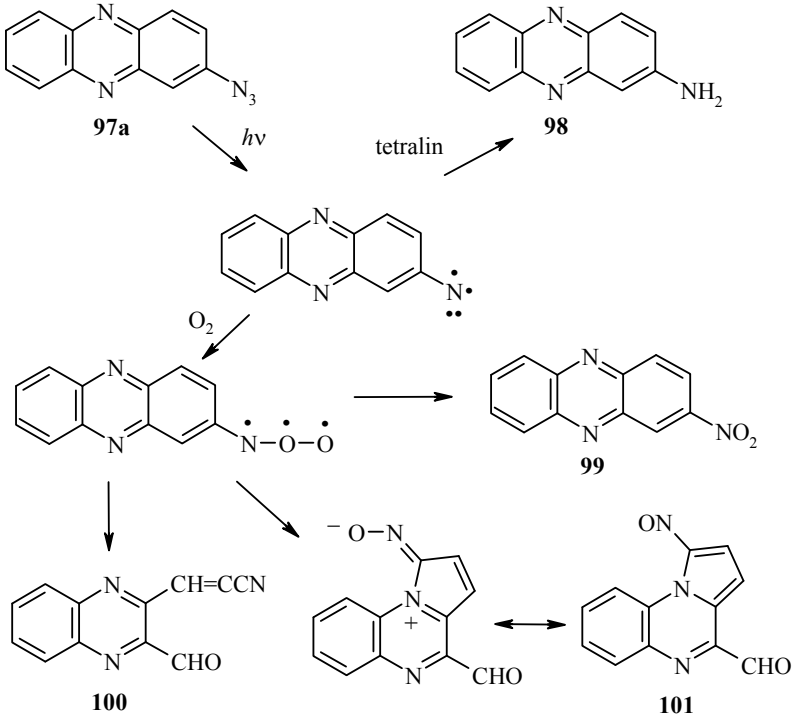
94–96 a R = $N(CH_2)_5$, **b** R = $N(CH_2CH_2)_2O$, **c** R = $N(CH_2)_4$, **d** R = 1-indolyl, **e** R = 3,5-dimethyl-1-pyrazolyl, **f** R = 3-methyl-5-phenyl-1-pyrazolyl, **g** R = 3-amino-4-methoxycarbonyl-1-pyrazolyl, **h** R = 3-amino-4-ethoxycarbonyl-1-pyrazolyl, **i** R = 3-amino-4-*n*-propoxycarbonyl-1-pyrazolyl, **j** R = 3-amino-4-isopropoxycarbonyl-1-pyrazolyl, **k** R = 3-amino-4-butoxycarbonyl-1-pyrazolyl, **l** R = 3-amino-4-(2-ethylhexyloxycarbonyl)-1-pyrazolyl, **m** R = $N(CH_2CH_2)_2CH_2$

Other Methods of Synthesis

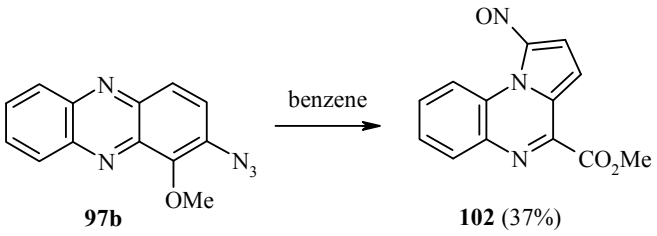
Under these methods of synthesis of pyrrolo[1,2-*a*]quinoxalines we include methods based either on condensed derivatives of quinoxaline (a) or on compounds containing neither a pyrrole ring nor a quinoxaline system (b). In method (b) the pyrroloquinoxaline system can be formed with the initial formation of the pyrrole ring (b-I) or the quinoxaline system (b-II). In this review we examine only the second version (b-II).

A typical example is the recyclization of isoxazolo[2,3-*a*]quinoxalines **95a-m** to pyrrolo[1,2-*a*]quinoxalines **96a-m** [46-48], shown in the scheme above.

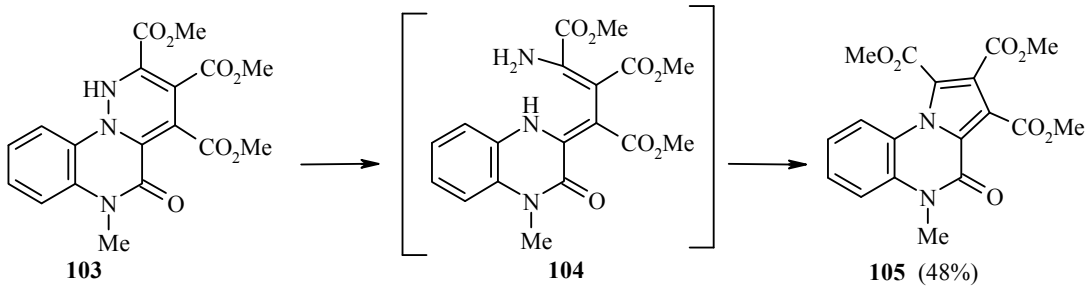
Investigation of the decomposition of 2-azidophenazine (**97a**) in various hydrocarbon solvents showed that the main product in all the solvents at 130-131°C is 2-aminophenazine (**98**). The same compound is readily obtained at room temperature in tetraline and decaline. In other solvents (hexane, cyclohexane, benzene, and xylene) saturated with oxygen 2-nitrophenazine (**99**), 3-[2-(3-formylquinoxalinyl)]acrylonitrile (**100**), and 4-formyl-1-nitroso-pyrrolo[1,2-*a*]quinoxaline (**101**) are formed, while in the absence of oxygen resinification occurs [52].



Under analogous conditions 2-azido-1-methoxyphenazine (**97b)** forms the derivative of pyrrolo-[1,2-*a*]quinoxaline **102**, but here the number of side products reaches six [53].

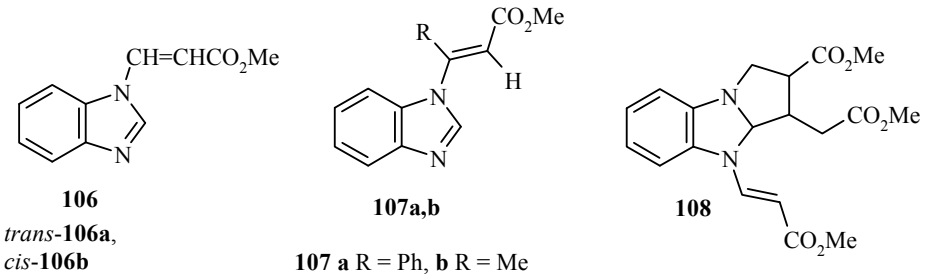


Another example of the modification of a tricyclic compound is the transformation of pyridazinoquinoxaline **103** in an acidic medium into the pyrroloquinoxaline **105** [54].



103 **104** **105** (48%)

The reaction of methyl propargylate (propiolate) with benzylimidazole and its 2-alkyl and aryl derivatives in acetonitrile leads to the formation of the methyl esters of 3-*trans*-(1-benzimidazolyl)acrylic acid **106a** and **107a**,**b**, whereas the reaction with benzimidazole in methanol leads exclusively to the corresponding *cis* isomer **106b**; in the absence of the solvent the treatment of benzimidazole with methyl propiolate gives a mixture of compounds **106a**,**b** and pyrrolo[1,2-*a*]benzimidazole **108**. At the same time the 2-isopropyl, 2-phenyl, and 2-benzyl derivatives of benzimidazole in reaction with methyl propiolate without a solvent form the pyrrolo[1,2-*a*]quinoxalines **114** and **115** [55].

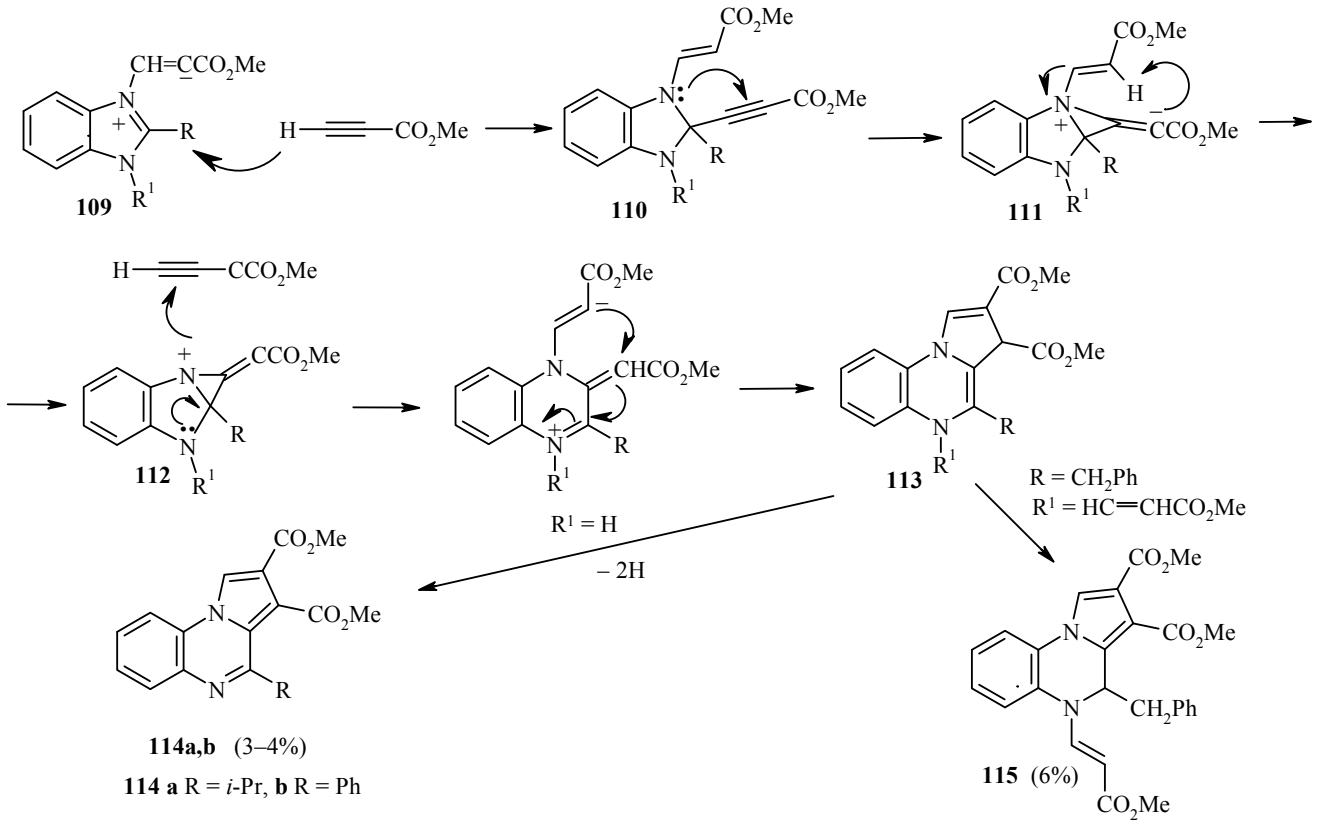


106
trans-**106a**,
cis-**106b**

107a,b

107 a R = Ph, **b** R = Me

108



109 **110** **111** **112** **113**

R^1 = H
– 2H

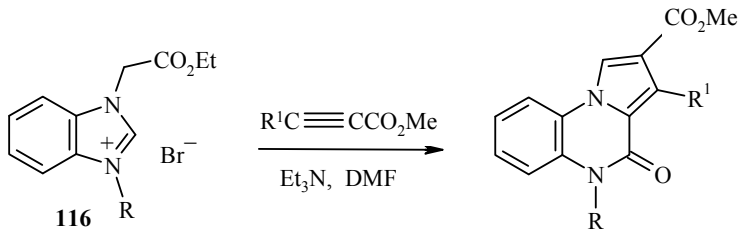
R = CH_2Ph
R^1 = HC═$CHCO_2Me$

114a,b (3–4%)
114 a R = *i*-Pr, **b** R = Ph

115 (6%)

The formation of the pyrrolo[1,2-*a*]quinoxalines can be represented by various schemes; according to one of them the zwitterion **109**, formed under the reaction conditions from the corresponding benzimidazole derivative, detaches a proton from the methyl propriolate with the generation of an acetylide anion, which in turn adds to the benzimidazole at position 2. As shown in the scheme, nucleophilic attack by the nitrogen atom at the triple bond generates a new carbanion. *cis*-Elimination of methyl propiolate (of the Chugaev type) from the intermediate **111** leads to compound **112** and methyl propiolate, recombination of which leads to the structure **113**. Aromatization of compound **113** with R^1 = H or prototropic isomerization of the tricycle **113** with R^1 = CH=CHCO$_2$Me gives compounds **114** and **115** respectively [55].

The benzimidazoles **116** are also transformed into pyrroloquinoxalines **117** by the action of acetylenecarboxylic acid derivatives [56-58].

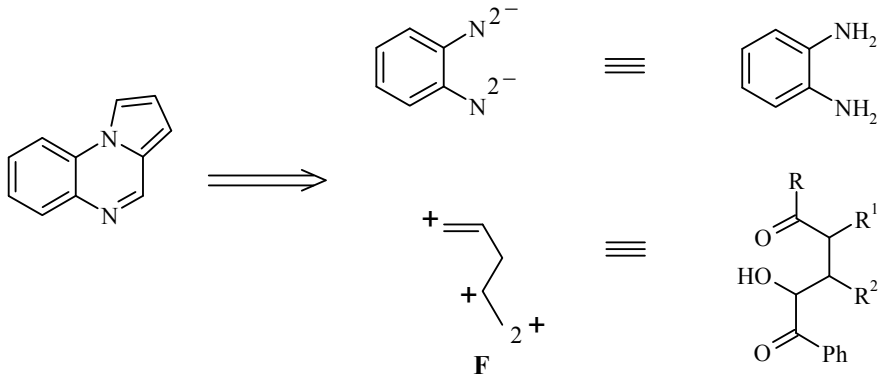


117a–f (41–50%)

117a–c R^1 = H, **a** R = Me, **b** R = Et, **c** R = Bu;
d–f R^1 = CO_2Me, **d** R = Me, **e** R = Et, **f** R = Pr

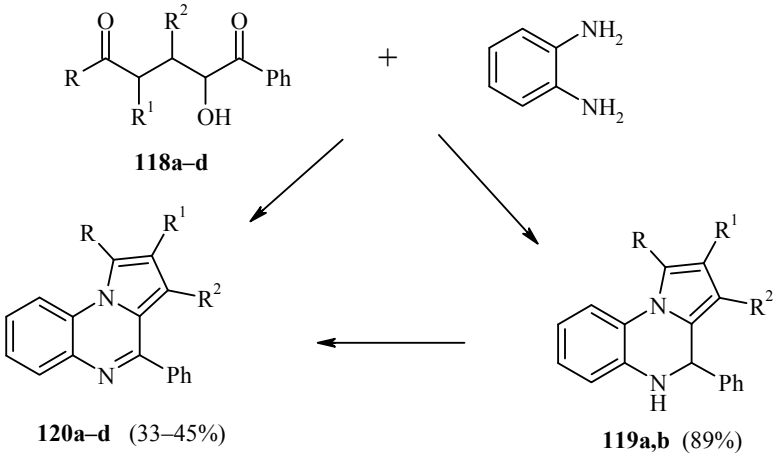
Economically favorable and ecologically harmless methods, which are in most cases one-pot tandem processes, occupy a special position among methods for the synthesis of condensed heterocyclic compounds.

As seen from the retrosynthetic analysis of the structure presented below, the simplest and most accessible reagent for the synthesis of pyrrolo[1,2-*a*]quinoxalines is *o*-phenylenediamine. If the aim is to synthesize a derivative of pyrrolo[1,2-*a*]quinoxaline from *o*-phenylenediamine the second reagent must be a compound with at least five carbon atoms having functional centers capable of reacting with the amino groups of the *o*-phenylenediamine at positions 1, 2, and 5.



F

Derivatives of 2-hydroxy-1,5-diketones **118a-d**, which are synthetic equivalents of synthon **F**, meet these requirements. The reaction of 2-hydroxy-1,5-diketones **118a-d** with *o*-phenylenediamine leads to the formation of derivatives of 4,5-dihydropyrrolo[1,2-*a*]quinoxaline **119a**,**b**, which are dehydrogenated by the action of MnO_2 to the corresponding derivatives of pyrrolo[1,2-*a*]quinoxaline **120a**,**b**. The use of 2-hydroxy-1,5-diketones **118c**,**d**, however, leads directly to the formation of pyrrolo[1,2-*a*]quinoxalines **120c**,**d** [59].



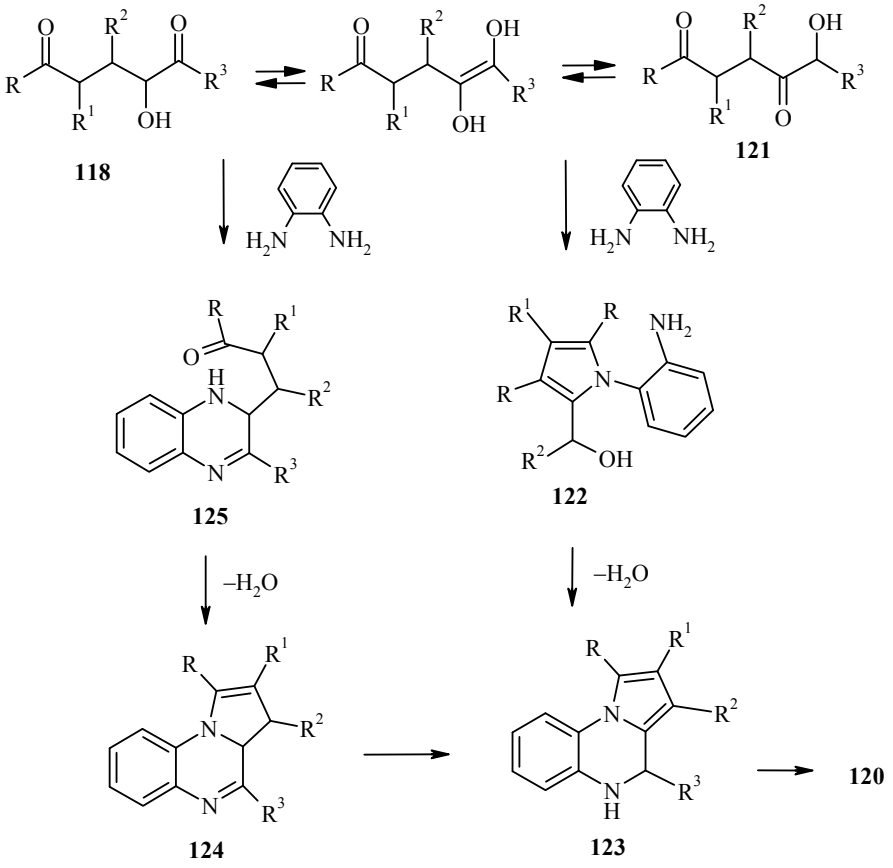
118a–d

120a–d (33–45%)

119a,b (89%)

118–120 a R = R^2 = Ph, R^1 = H, **b** R + R^1 = $(CH_2)_4$, R^2 = Ph;
118, 120 c R = Ph, R^1 = H, R^2 = Me, **d** R = Ph, R^1 = R^2 = H

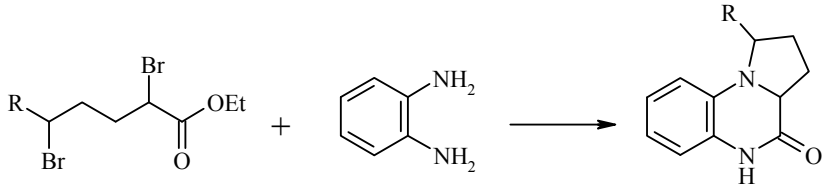
The formation of the pyrrolo[1,2-*a*]quinoxaline structure in this reaction can be represented in one of two ways: a) Isomerization of the 2-hydroxy-1,5-diketone **118** to the 5-hydroxy-1,4-diketone **121** with the subsequent formation of the *ortho*-aminophenylpyrrole **122** and closure of the dihydroquinoxaline structure **123**; b) Reaction of the α-hydroxyketone fragment with *o*-phenylenediamine with the formation of the hydroquinoxaline derivative **125** and subsequent closure of the dihydropyrrole ring and isomerization of the 3,3a-dihydropyrrolo[1,2-*a*]quinoxaline structure **124** to the more stable 4,5-dihydropyrrolo[1,2-*a*]quinoxaline structure **123**.



118 **121** **125** **122** **124** **123** **120**

The second path seems more likely since during the reaction of the hydroxydiketone with *o*-phenylenediamine in a 15:1 mixture of ethanol and acetic acid and subsequent oxidation a mixture of compound **120** and the quinoxaline derivative **125** in a ratio of 2:5 is formed.

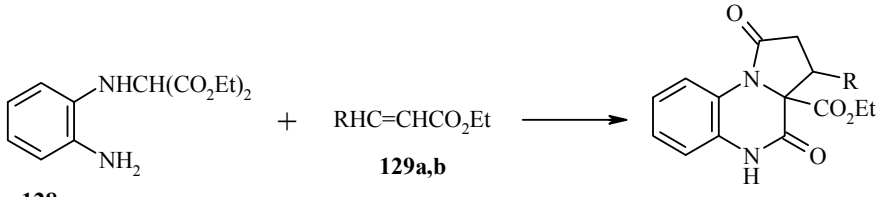
The reaction of *o*-phenylenediamine with the α,δ-dihalo carboxylic acids **126a-c** leads to annelation of the pyrrolo[1,2-*a*]pyrazine system and the formation of 1,2,3,4-tetrahydropyrroloquinoxalinones **127a-c** [60, 61].



126a–c **127a–c**

126, 127 a R = H, **b** R = Me, **c** R = CO_2Et

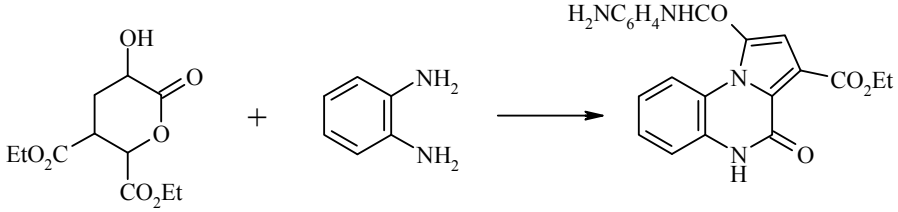
The authors of [62, 63] described the construction of the tricycle **130a**,**b** as the result of condensation of the *o*-phenylenediamine derivative **128** with the ethyl acrylates **129a**,**b**.



128 **129a,b** **130a,b** (60%)

129, 130 a R = H, **b** R = Me

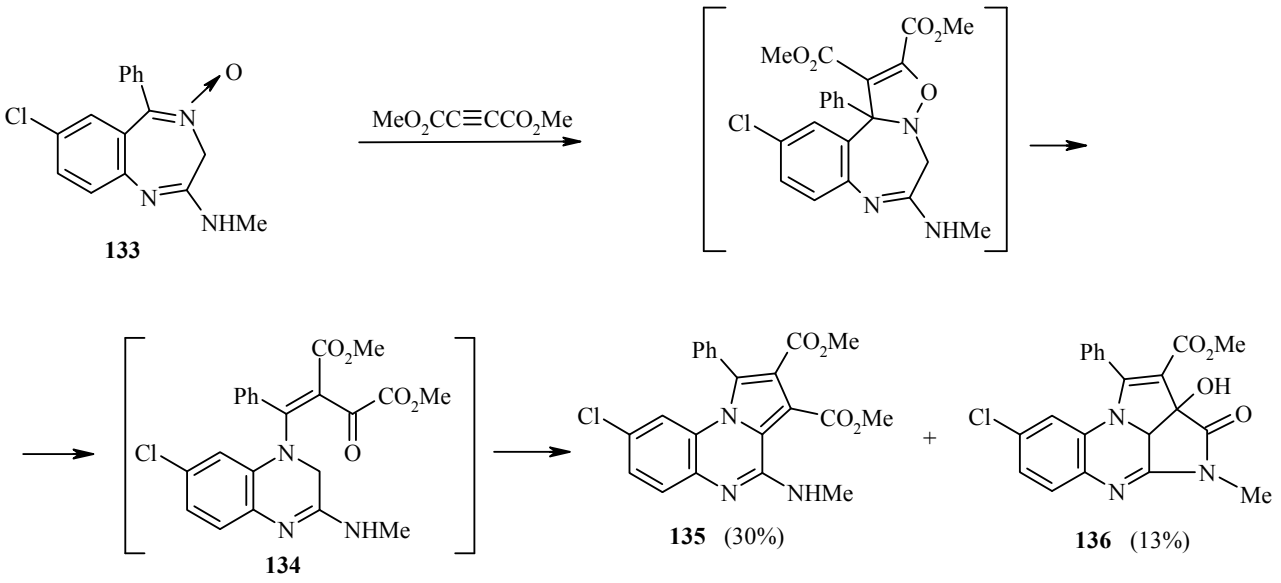
The 3-hydroxypyrone **131** is also converted by the action of *o*-phenylenediamine into a derivative of pyrroloquinoxalines **132** [64].



131 **132** (5%)

The N-oxides not only of quinoxalines but also of 1,4-benzodiazepines can serve as excellent 1,3-dipoles in the synthesis of derivatives of pyrrolo[1,2-*a*]quinoxalines. For example, the reaction of chlorodiazepine oxide **133** with dimethyl acetylenedicarboxylate takes place by a scheme of 1,3-dipolar addition with the formation of two types of tri- and tetracyclic derivatives of pyrrolo[1,2-*a*]quinoxalines **135** and **136** [65].

The intermediate formation of compound **134**, which is converted into compounds **135** and **136** as a result of intramolecular cyclocondensations, is explained by a Beckmann-type rearrangement in the adduct formed at the first stage of 1,3-cycloaddition.



CONCLUSION

According to the data in Table 1, of the 12 possible methods for the synthesis of pyrrolo[1,2-*a*]quinoxalines the most successful are the methods based on the **A1**, **B1**, **C1**, **C2**, and **E2** approaches. Methods based on **A2**, **A3**, **A4**, and **B2** can only be realized after effective methods have been developed for the synthesis of N-alkylated derivatives of quinoxalines with alkyl fragments of various lengths and with various functional groups at the terminal atoms of the alkyl fragment that promote closure of the pyrrole ring, or with participation of the C-2 atom of the quinoxaline system, or with participation of the substituent at position 2 of the quinoxaline system.

TABLE 1. Possible and Implemented Methods of Synthesis of Pyrrolo[1,2-*a*]quinoxalines Based on Derivatives of Quinoxalines

	Possible	Implemented (number of papers)
A	**A1**, **A2**, **A3**, **A4**	**A1** (16), **A2** (0), **A3** (0), **A4** (0)
B	**B1**, **B2**, **B3**	**B1** (2), **B2** (0), **B3** (1)
C	**C1, C2**	**C1** (16), **C2** (5)
D	**D**	**D** (4)
E	**E1**, **E2**	**E1** (1), **E2** (6)

REFERENCES

1. G. W. H. Cheeseman and R. F. Cookson, *Condensed Pyrazines*, John Wiley and Sons, New York, 1979.
2. I. Kumashiro, *Nippon Kagaku Zasshi*, **82**, 1068 (1961); *Chem. Abstr*., **59**, 621 (1963).
3. G. W. H. Cheeseman and P. D. Roy, *J. Chem. Soc.* (*C*), 856 (1969).
4. E. C. Taylor and E. S. Hand, *J. Am. Chem. Soc*., **85**, 770 (1963).
5. E. C. Taylor and M. E. S. Hand, *Tetrahedron Lett*., **25**, 1225 (1962).
6. J. L. Nelson and J. H. Boyer, *J. Am. Chem. Soc*., **72**, 2980 (1950).

7. K. Okumura and K. Shigemitsu, Jpn. Pat., 67, 20, 069 (1965); *Chem. Abstr.*, **69**, 19217 (1968).
8. G. W. H. Cheeseman and P. D. Roy, *J. Chem. Soc*., *C*, 2848 (1968).
9. G. W. H. Cheeseman and B. Tuck, *J. Chem. Soc*., 3678 (1965).
10. K. Matoba, K. Itoh, M. Nagata, and T. Yamazaki, *Heterocycles*, **14**, 465 (1980).
11. K. Matoba, K. Itoh, K. Kondo, T. Yamazaki, and M. Nagata, *Chem. Pharm. Bull.*, **29**, 2442 (1981).
12. K. Matoba, Yu. Miyata, and T. Yamazaki, *Chem. Pharm. Bull.*, **31**, 476 (1983).
13. K. Matoba, T. Terada, M. Sugiura, and T. Yamazaki, *Heterocycles*, **26**, 55 (1987).
14. A. Atfah, M. Y. Abu-Shuheil, and J. Hill, *Tetrahedron*, **46**, 6483 (1990).
15. V. A. Mamedov, A. A. Kalinin, A. T. Gubaidullin, I. A. Litvinov, N. M. Azancheev, and Ya. A. Levin, *Zh. Org. Khim.*, **40**, 123 (2004).
16. M. Armengol and J. A. Joul, *J. Chem. Soc.*, *Perkin Trans. 1*, 978 (2001).
17. N. S. Prostakov, in: *Catalytic Synthesis and Transformations of Heterocyclic Compounds. Heterogeneous Catalysis* [in Russian], Zinatne, Riga (1976), p. 68.
18. V. G. Pleshakov, Md. Zainul Abedin, N. D. Sergeeeva, and N. S. Prostakov, *Zh. Org. Khim.*, **19**, 667 (1983).
19. R. G. Glushkov, L. N. Dronova, A. S. Elina, I. S. Musatova, M. V. Porokhovaya, N. P. Solov'eva, V. V. Chistyakov, and Yu. N. Shvenker, *Khim.-Farm. Zh.*, **22**, 336 (1988).
20. F. Eiden and G. Bachmann, *Arch. Pharm*., **306**, 876 (1973).
21. W. Kiel and F. Kröhnke, *Chem. Ber*., **105**, 3709 (1972).
22. V. G. Kaupp, H. Voss, and H. Frey, *Angew. Chemie*, **99**, 1327 (1987).
23. L. H. Flett and W. H. Gardner, *Maleic Anhydride Derivatives*, John Wiley and Sons, Inc., New York, N. Y., 1952.
24. A. Schonberg and A. Mustafa, *J. Chem. Soc*., 654 (1943).
25. E. C. Taylor and G. W. H. Cheeseman, *J. Am. Chem. Soc*., **86**, 1830 (1964).
26. A. Berlin, S. Martina, G. Pagani, G. Schiavon, and G. Zotti, *Heterocycles*, **32**, 85 (1991).
27. Yv. Blache, A. Gueiffier, A. Elhakmaoui, H. Viols, and J. P. Chapat, *J. Heterocycl. Chem*., **32**, 1317 (1995).
28. J. Guillon, M. Boulouard, V. Lisowski, S. Stiebing, V. Lelong, P. Dallemagne, and S. Rault, *J. Pharm. Pharmacol.*, **52**, 1369 (2000); *Ref. Zh. Khim.*, 17Zh253 (2001).
29. R. Buchan, M. Fraser, and P. V. S. K. T. Lin, *J. Org. Chem*., **50**, 1324 (1985).
30. J. Guillon, Luochani-Raoul, M. Boulouard, P. Dallemagne, M. Daoust, and S. Rault, *Pharm. Pharmacol. Commun*, **4**, 319 (1998); *Ref. Zh. Khim.*, 24Zh374 (1998).
31. I. A. Tolmacheva, I. V. Mashevskaya, and A. N. Maslivets, *Zh. Org. Khim.*, **38**, 303 (2002).
32. K. S. Bozdyreva, I. V. Smirnova, and A. N. Maslivets, *Zh. Org. Khim.*, **41**, 1101 (2005).
33. A. I. Maslivets, I. V. Mashevskaya, S. V. Kol'tsova, A. V. Duvalov, and V. P. Feshin, *Zh. Org. Khim.*, **38**, 775 (2002).
34. Yu. S. Andreichikov (editor), *Chemistry of Five-Membered 2,3-Dioxoheterocycles* [in Russian], Perm (1994), p. 93.
35. H. W. Heine and R. P. Henzel, *J. Org. Chem.*, **34**, 171 (1969).
36. W. K. Easley and C. T. Bahner, *J. Am. Chem. Soc*., **72**, 3803 (1950).
37. Z. Zhou, Y. Hu, and H. Hu, *Synth. Commun*., **28**, 3397 (1998).
38. J. Zhou, L. Zhang, Yu. Hu, and H. Hu, *J. Chem. Res. Synop*., 552 (1999).
39. M. Komatsu, Yu. Kassano, S. Yamaoka, and S. Minakata, *Synthesis*, 1398 (2003).
40. W. D. Ollis and S. P. Stanforth, *J. Chem. Soc.*, *Perkin Trans*. 1, 945 (1989).
41. J. W. Lown and K. Matsumoto, *Can. J. Chem*., **49**, 1165 (1971).
42. J. W. Lown and K. Matsumoto, *Can. J. Chem*., **49**, 3119 (1971).
43. C. H. Weidner, F. M. Michaels, D. J. Beltman, and C. J. Montgomery, *J. Org. Chem*., **56**, 5594 (1991).

44. J. G. Smith and E. M. Levi, *J. Organomet. Chem.*, **36**, 215 (1972).
45. A. F. Khlebnikov, E. I. Kostik, Yu. Kopf, E. V. Aleksandrov, and R. R. Kostikov, *Zh. Org. Chem.*, **34**, 754 (1998).
46. H. S. Kim, Y. Kurasawa, C. Yoshii, M. Masuyama, and A. Takada, *J. Heterocyclic Chem*, **27**, 1119 (1990).
47. H. S. Kim, S. H. Nam, and Y. Kurasawa, *Taehan Hwahakhoe Chi*, **34**, 469 (1990); *Chem. Abstr*., **114**, 101935 (1991).
48. H. S. Kim, Y. Kurasawa, and A. Takada, *J. Heterocycl. Chem.*, **26**, 871 (1989).
49. H. S. Kim, Yo. Kurasawa, C. Yoshii, M. Masuyama, and A. Takada, *J. Heterocycl. Chem*, **27**, 1115 (1990).
50. H. S. Kim, S. U. Lee, W. Y. Jeong, S. W. Han, D. I. Kim, and Yo. Kurasawa, *J. Korean Chem. Soc.*, **45**, 318 (2001).
51. H. S. Kim, S. T. Kwag, and K. O. Choi, *J. Heterocycl. Chem.*, **37**, 103 (2000).
52. G. F. Bettinetti, E. Fasani, G. Minoli, and S. Pietra, *Gazz. Chim. Ital.*, **109**, 175 (1979).
53. A. Albini, G. Bettinetti, G. Minoli, *J. Org. Chem*., 1245 (1987).
54. P. J. Abbott, R. M. Acheson, M. W. Foxton, N. R. Raulins, and G. E. Robinson, *J. Chem. Soc.*, *Perkin Trans. 1*, **17**, 2182 (1972).
55. R. M. Acheson and M. S. Verlander, *J. Chem. Soc.*, *Perkin Trans. 1*, 2348 (1973).
56. D. A. Rowland and J. B. Taylor, Pat. Ger. Offen. 2816109; *Chem. Abstr*., **90**, 72232 (1979).
57. O. Meth-Gohn, *Tetrahedron Lett*, **16**, 413 (1975).
58. I. A. Ager, A. C. Barnes, G. W. Danswan, P. W. Hairsine, D. P. Kay, P. D. Kennewell, S. S. Matharu, P. Miller, P. Robson, D. A. Rowlands, W. R. Tully, and R. Westwood, *J. Med. Chem.*, **31**, 1098 (1988).
59. V. A. Kaminskii, T. V. Moskovkina, and S. V. Borodina, *Khim. Geterotsikl. Soedin.*, 112 (1992). [*Chem. Heterocycl. Comp*., **28**, 104 (1992)].
60. A. M. Likhosherstov, L. S. Nazarova, and A. P. Skoldinov, Fr. Pat., 1510781 (1968); *Chem. Abstr*., **70**, 68427 (1969).
61. Scientific-Research Institute of Pharmacology and Chemotherapy., Brit. Pat., 1144749 (1969); *Chem. Abstr*., **70**, 106558 (1969).
62. M. Artico, V. Nacci and G. De Martino, *Ann. Chim*., **57**, 1431 (1967); *Chem. Abstr*., **68**, 105157 (1968).
63. M. Artico, V. Nacci and G. De Martino, *Ann. Chim*., **58**, 136 (1968); *Chem. Abstr*., **69**, 36072 (1968).
64. I. Kumashiro, *Nippon Kagaku Zasshi*, **82**, 934 (1961); *Chem. Abstr*., **57**, 12489 (1962).
65. T. Miyadera, Yo. Kawano, T. Hata, C. Tamura, and R. Tachikawa, *Chem. Pharm. Bull.*, **25**, 3247 (1977).