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

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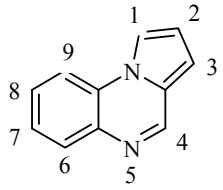
Published data on methods for the synthesis of pyrrolo[1,2-a]quinoxalines, based on derivatives of pyrroles and also on compounds not originally derivatives of quinoxalines or pyrroles, are reviewed and classified.

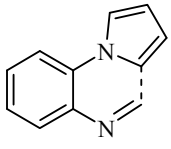
Keywords: pyrroles, pyrrolo[1,2-*a*]quinoxalines.

In a continuation of the previous review [1], where possible methods for the construction of pyrrolo-[1,2-*a*]quinoxalines based on quinoxalines were examined, data are presented here on methods of synthesis based on pyrroles and other systems that are not derivatives of either quinoxalines or pyrroles.



Pyrrolo[1,2-*a*]quinoxalines

Various possible methods based on pyrroles for the construction of the pyrrolo[1,2-*a*]quinoxaline system are given below.



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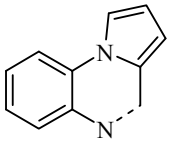

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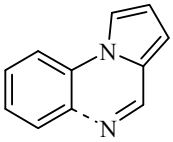

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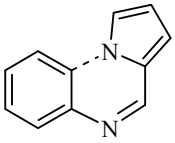

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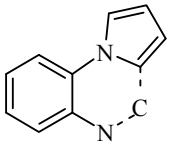

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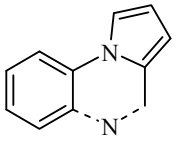

B2

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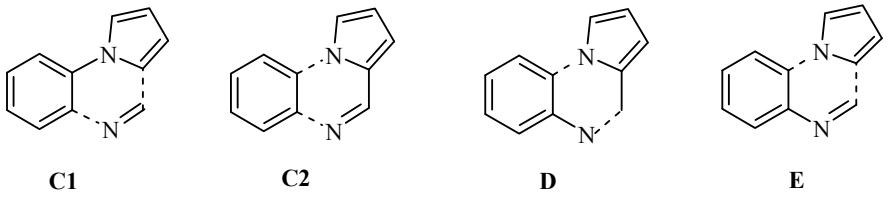
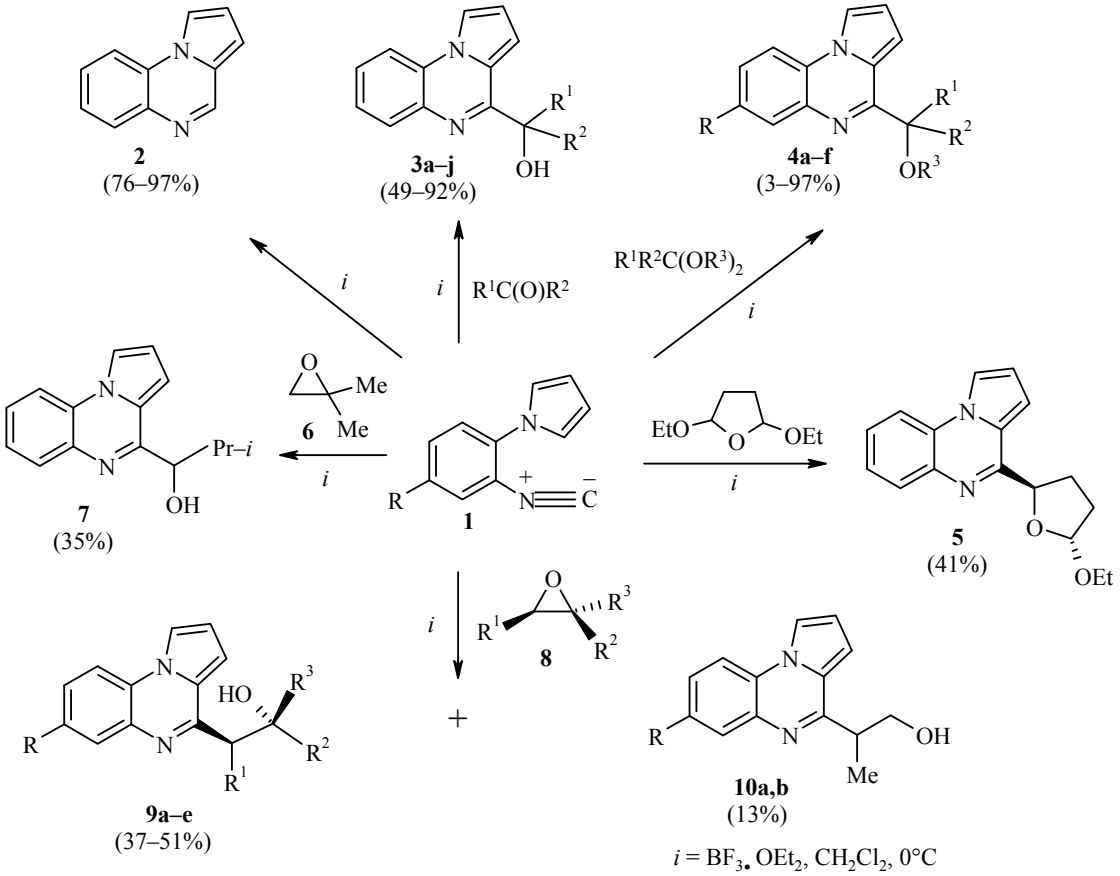


C1 **C2** **D** **E**

Type A1 Production Methods

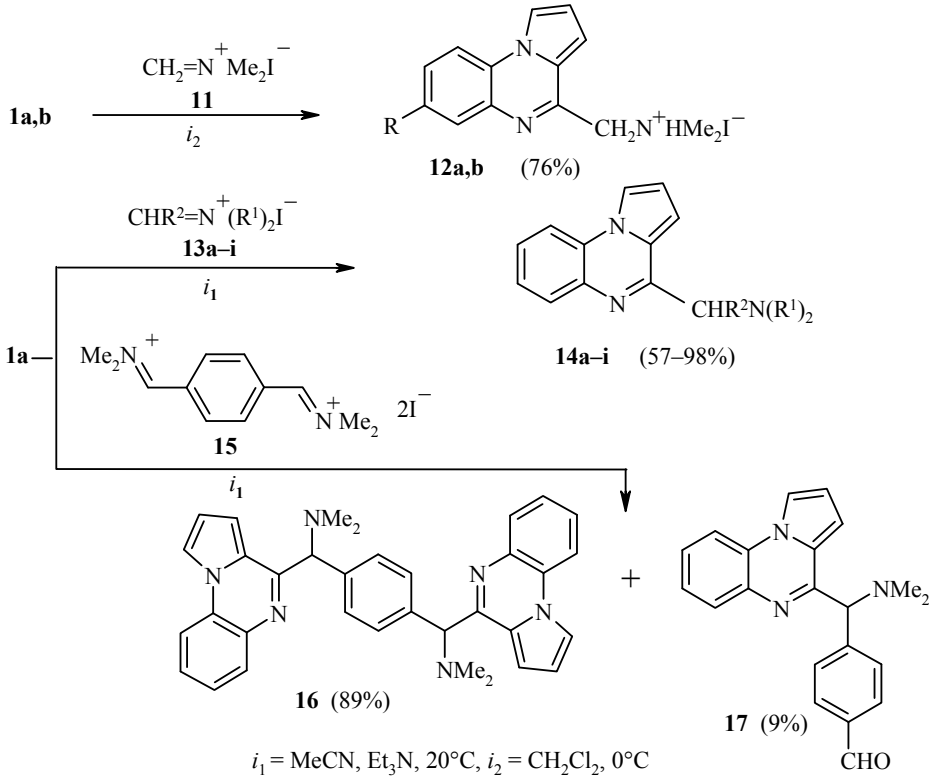
A strategy for the synthesis of pyrrolo[1,2-*a*]quinoxalines based on pyrrole derivatives can be developed on the basis of the structural components used for the formation of the pyrazine ring. The principles represented by the symbol **A1** originating from retrosynthetic analysis, i.e., the cyclocondensation of 1-aryl derivatives of pyrrole containing N–C fragments at the *ortho* position of the aryl substituent, are most often used. An example of a synthesis using such an approach is the intramolecular cyclization of 1-(2-isocyano-phenyl)pyrrole (**1a**), which is easily obtained by dehydration of the corresponding formylamino derivative with



1 a R = H, **b** R = Me; **3 a–e** R^2 = H, **a** R^1 = Et, **b** R^1 = 2-Pr, **c** $R^1 = CMe_2Et$, **d** R^1 = Ph, **e** R^1 = 2-furyl; **f** $R^1 = R^2$ = Me; **g** $R^1+R^2 = (CH_2)_6$; **h** R^1 = Ph, R^2 = Me; **i** R^1 = Me, $R^2 = CO_2Et$; **j** R^1 = Me, $R^2 = (CH_2)_2CO_2Et$; **4 a** R = R^2 = H, $R^1 = R^3$ = Me; **b** R = R^2 = H, R^1 = Me, R^3 = Et; **c** R = H, $R^1 = R^2$ = Me, R^3 = Et, **d** R = R^2 = H, R^1 = vinyl, R^3 = Et, **e** R = R^2 = H, R^1 = Ph, R^3 = Me; **f** R = R^1 = Me, R^2 = H, R^3 = Et; **9 a** R = $R^1 = R^2$ = H, R^3 = Me; **b** R = $R^1 = R^2$ = H, R^3 = Ph; **c** R = R^3 = H, $R^1+R^2 = (CH_2)_4$; **d** R = $R^1 = R^2$ = H; $R^3 = (CH_2)_2CH{=}CH_2$; **e** R = Me, $R^1+R^2 = (CH_2)_4$, R^3 = H; **10 a** R = H, **b** R = Me

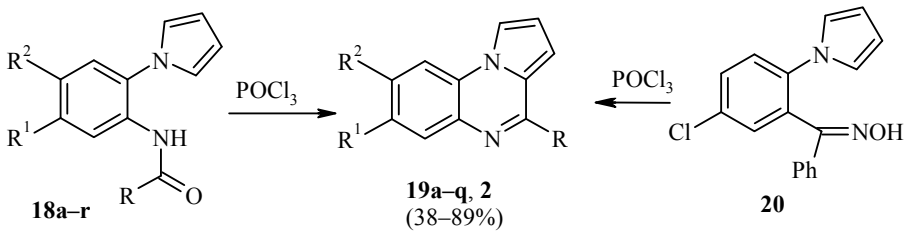
a $POCl_3/Et_3N$ mixture in THF. The reaction takes place in the presence of catalytic amounts of boron trifluoride etherate under mild conditions (CH_2CH_2, 0°C), resulting in the formation of unsubstituted pyrrolo[1,2-*a*]quinoxaline (**2**) with an almost quantitative yield [2, 3]. The cyclization of compound **1** catalyzed by boron trifluoride etherate also goes well in the presence of various aldehydes and ketones [2, 3], semiacetals [2], and 2,5-diethoxytetrahydrofuran [2] and by the action of various epoxides [2]; here, various derivatives of pyrrolo[1,2-*a*]quinoxalines **2**-**5**, **7**, and **9** substituted at position 4 are formed with yields of 3-97%, depending on the employed carbonyl component [2, 3].

The reaction of 1-(2-isocyanoaryl)pyrroles with Eschenmoser's salt **11** also goes smoothly with the formation of dimethyl(pyrrolo[1,2-*a*]quinoxalin-4-ylmethyl)ammonium iodides **12**, which after treatment with an aqueous solution of $NaHCO_3$ readily give quantitative yields of the free bases. In the case of the reactions of 1-(2-isocyanophenyl)pyrroles **1a**,**b** with other salts of the iminium type **13** and **15**, obtained from secondary amines and aldehydes in the presence of $Me_3SiCl/NaI/Et_3N$, it was shown that such a synthesis of 4-(1-dialkylaminoalkyl)pyrrolo[1,2-*a*]quinoxalines **14**, **16**, and **17** is universal [4].



1, **12 a** R = H, **b** R = Me, **13**, **14 a** R^1 = Me, R^2 = Et, **b** $R^1 = (CH_2)_5$, R^2 = *i*-Pr, **c** R^1 = Me, R^2 = *t*-Bu, **d** R^1 = Me, R^2 = Ph, **e** $R^1 = (CH_2)_4$, R^2 = Ph, **f**–**i** R^1 = Me, **f** R^2 = 4-$MeOC_6H_4$, **g** R^2 = 4-$O_2NC_6H_4$, **h** R^2 = 2-furyl, **i** R^2 = 4-ClC_6H_4

During the construction of the pyrazine ring of the pyrrolo[1,2-*a*]quinoxaline system the direct source of the N–C fragment can be not only an isocyano function ($-N^+\equiv C^-$) but also an acylamino function (–NHC(O)R) [3, 5-10]. As a result as far back as 1966 a general method was proposed for the production of pyrrolo[1,2-*a*]quinoxalines [5] by the cyclization of 1-(2-aminophenyl)pyrroles, obtained by the Clauson-Kaas reaction [11], and their derivatives **18**. The cyclization of the acylamines **18** takes place during the action of phosphorus oxychloride.



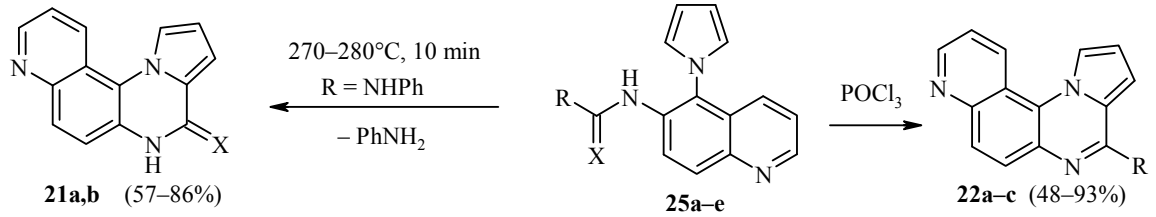
18a–r **19a–q**, **2** (38–89%) **20**

18, **19 a–d** $R^1 = R^2 = H$, **a** R = Me, **b** R = NHPh, **c** R = Ph, **d** R = CH_2Cl; **e** R = Ph, R^1 = Cl, R^2 = H; **f–k** $R^1 = CF_3$, R^2 = H, **f** R = CH_2Cl, **g** R = Bu, **h** R = $CH_2CH{=}CHMe$, **i** R = C_6H_{13}, **j** R = $CH_2CH{=}CHPr$, **k** R = $(CH_2)_2C_6H_3(OCH_2O)$-3,4; **l–o** R^1 = OMe, R^2 = H; **l** R = Me, **m** R = Bu, **n** R = C_6H_{13}, **o** R = $CH_2CH{=}CHPr$; **p**, **r** R^1 = H, R^2 = OMe, **p** R = $CH_2CH{=}CHMe$, **q** R = $CH_2CH{=}CHPr$; **18r, 2** $R = R^1 = R^2 = H$

It was unexpectedly found [6] that *o*-(pyrrol-1-yl)benzophenone oxime **20**, which undergoes a Beckmann rearrangement to 5-chloro-2-(pyrrol-1-yl)benzanilide (**18e**) during the action $POCl_3$ in DMF, can serve as a starting material for the production of the pyrroloquinoxaline **19e**. The structure of the pyrroloquinoxaline **19e** was confirmed unambiguously not only spectrally but also by an alternative synthesis from the authentic 5-chloro-2-(pyrrol-1-yl)benzanilide (**18e**) by the method in [5].

Similarly, condensed derivatives of pyrrolo[1,2-*a*]quinoxalines **21-24** were obtained from 5-(pyrrol-1-yl)-quinolines **25** [12], 3-(pyrrol-1-yl)dibenzofurans **26** [13], and 3-(pyrrol-1-yl)carbazole **27** [14] containing at positions 6, 2, and 4 respectively, the functional group RC(X)NH, which was introduced by condensation of the corresponding amines with acetic anhydride, phenyl isocyanate, phenyl isothiocyanate, and aliphatic isothiocyanates.

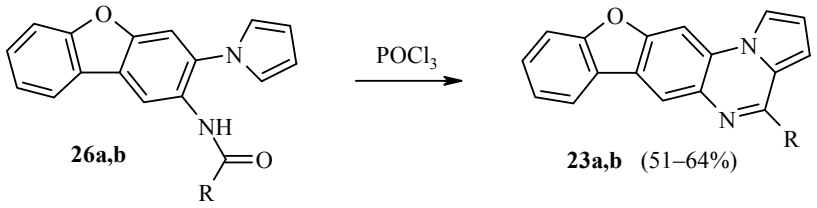
Closure of the pyrazine ring in compounds **25a-c** is achieved by heating in the presence of $POCl_3$. Cyclization of compounds **25d**,**e** to pyrroloquinoxalines **21a**,**b** occurs in a boiling toluene solution for 1.5-2 h and during brief thermolysis respectively [12].



21a,b (57–86%) **25a–e** **22a–c** (48–93%)

21 a X = S, **b** X = O; **22 a** R = Me, **b** R = NHPh, **c** R = CH_2Bu-*t*; **25 a–c** X = O, **a** R = Me, **b** R = NHPh, **c** R = CH_2Bu-*t*; **d** X = S, R = NHPh; **e** X = O, R = NHPh

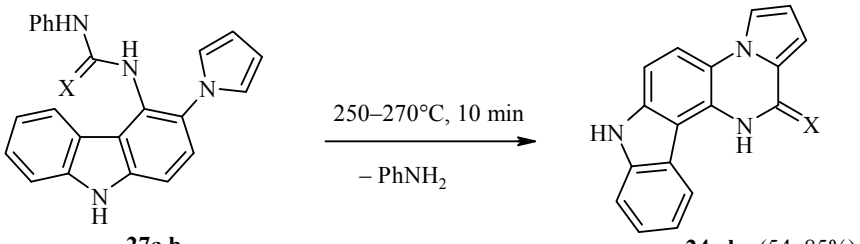
The pyrazine ring in 2-pyrrolyldibenzofurans **26** is also formed by heating in the presence of $POCl_3$ [13].



26a,b **23a,b** (51–64%)

23, **26 a** R = Me, **b** R = Ph

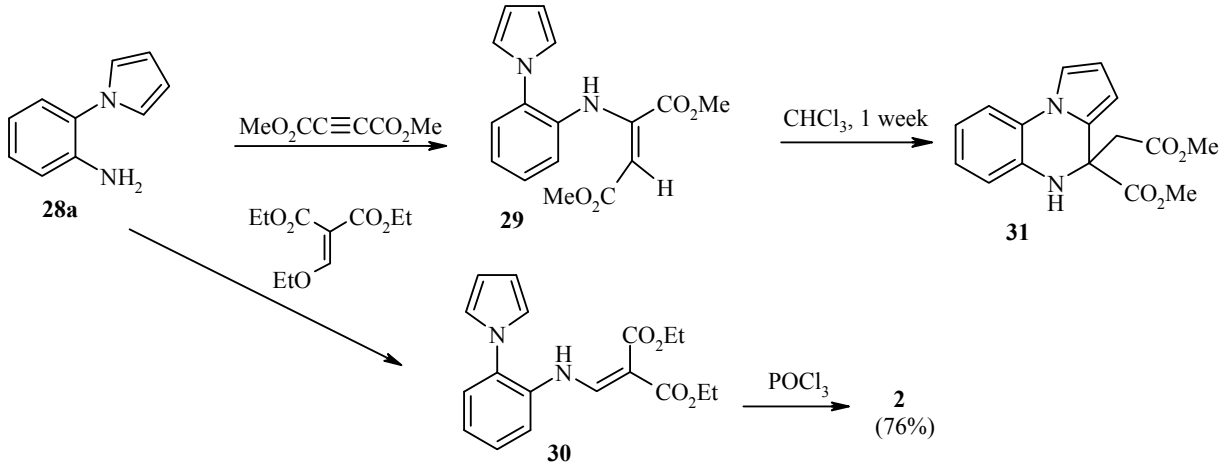
Closure of the pyrazine ring in the pyrrolylcarbazole **27** occurs during brief thermolysis at a temperature above 200°C [14].



27a,b **24a,b** (54–85%)

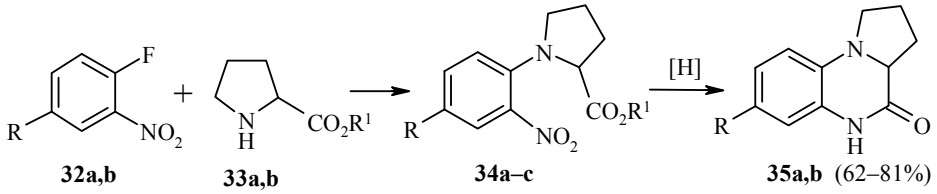
24, **27 a** X = S, **b** X = O

The cyclization of dimethyl [2-(pyrrol-1-yl)anilino]fumarate (**29**), obtained by the reaction of N-(2-aminophenyl)pyrrole (**28a**) with dimethyl acetylenedicarboxylate for a week in boiling chloroform, leads to methyl 4-(2-methoxy-2-oxoethyl)pyrrolo[1,2-*a*]quinoxaline-4-carboxylate (**31**). At the same time diethyl [2-(pyrrol-1-yl)anilino]methylenemalonate (**30**), easily obtained from N-(2-aminophenyl)pyrrole (**28a**) in reaction with diethyl ethoxymethylenemalonate in boiling $POCl_3$, is transformed after 15 min into pyrrolo[1,2-*a*]quinoxaline (**2**) [15].



Type A2 Production Methods

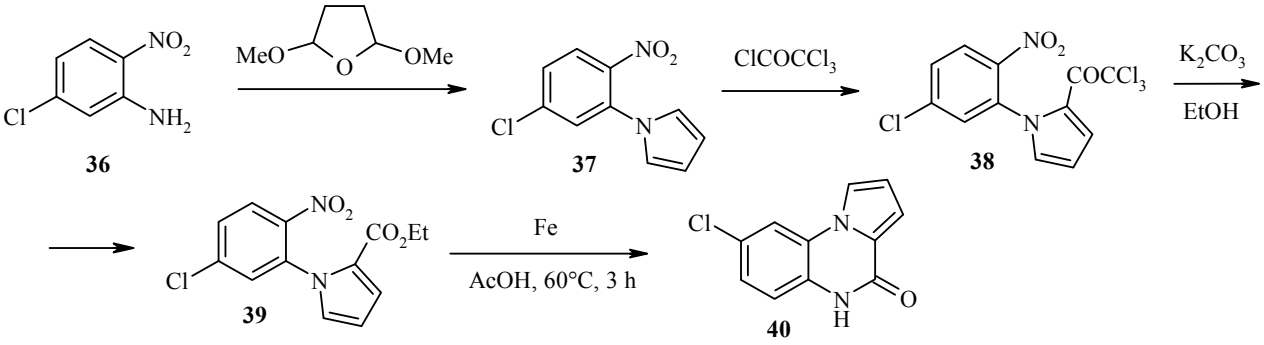
There is only one method of realizing a synthesis of type **A2**, and this involves reduction of the esters of N-(2-nitrophenyl)pyrrolidine-2-carboxylic acid **34** or the esters of N-(2-nitrophenyl)pyrrole-2-carboxylic acid **39**. Compounds **34** were obtained by the condensation of 1-fluoro-2-nitrobenzenes **32** with pyrrolidine-2-carboxylic acid (**33a)** or its ester **33b** [16-18] in boiling ethanol in the presence of $NaHCO_3$. The reductive cyclization of compounds **34** and **35** was realized both with cyclohexene in boiling ethanol in the presence of 10% Pd/C [16] and with iron powder in acetic acid [17, 18] and also for compound **34a** with sodium dithionite in water [17].



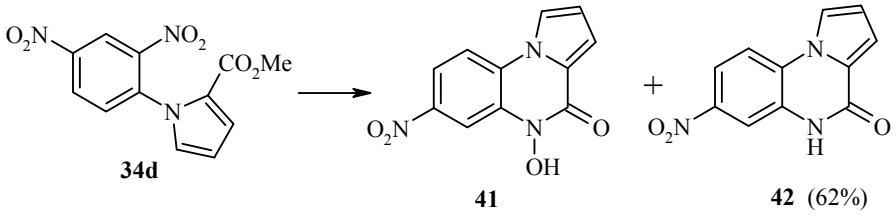
32a,b **33a,b** **34a–c** **35a,b** (62–81%)

32 a R = H, **b** R = NO_2; **33 a** R^1 = H, **b** R^1 = Me; **34 a** R = R^1 = H, **b** R = H, R^1 = Me, **c** R = NO_2, R^1 = H; **35 a** R = H, **b** R = NO_2

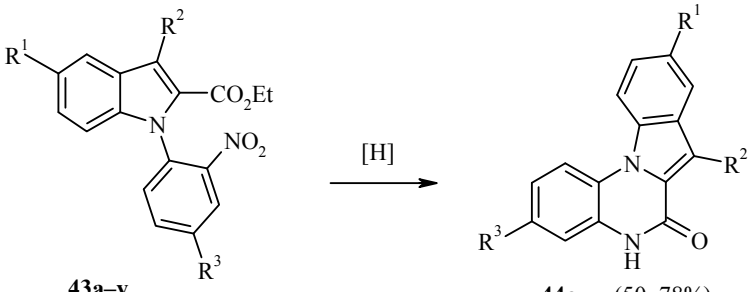
A method for the synthesis of the derivative of N-(2-nitrophenyl)pyrrolidine-2-carboxylic acid **39** involves alcoholysis of 1-(5-chloro-2-nitrophenyl)-2-trichloroacetyl-1H-pyrrole (**38**), which is in turn obtained as a result of a two-stage process from 5-chloro-2-nitroaniline (**36**) [19]. In this case reductive cyclization is realized successfully with iron powder in acetic acid (60°C, 3 h).



If ammonium sulfide is used as reducing agent a mixture of tetrahydropyrroloquinoxaline **42** and the N-hydroxy derivative **41** is formed from the arylpyrrolidine **34d** (R = NO_2, R^1 = Me) [20].



This approach has found use in the synthesis of condensed heterocyclic systems with a hydrogenated pyrrolo[1,2-*a*]quinoxaline fragment **44** [21-23].

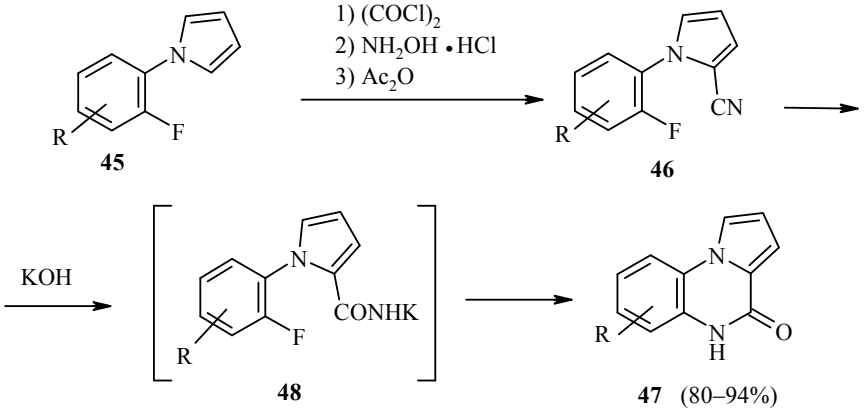


Compounds **43**, **44**	R^1	R^2	Compounds **43**, **44**	R^1	R^2	Compounds **43**, **44**	R^1	R^2
a	Me	H	**j**	Ph	H	**r**	Me	OMe
b	Me	Me	**k**	H	Ph	**s**	Me	OEt
c	Me	OMe	**l**	Me	Ph	**t**	Me	Cl
d	Me	OEt	**m**	OMe	Ph	**u**	Ph	H
e	Me	Cl	**n**	OEt	Ph	**v**	Ph	Me
f	Ph	H	**o**	Cl	Ph	**w**	Ph	OMe
g	Ph	OMe	**p**	Me	H	**x**	Ph	OEt
h	Ph	OEt	**q**	Me	Me	**y**	Ph	Cl
i	Ph	Cl						

43, **44 a–j** R^3 = Cl, **k–o** R^3 = H; **43 p–y** R^3 = NO_2; **44 p–y** R^3 = NH_2

Type A3 Production Methods

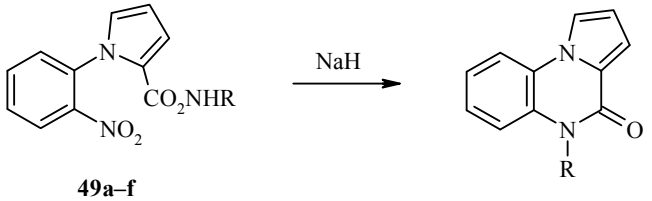
The key stage in the synthesis of pyrrolo[1,2-*a*]quinoxalines **47** by type **A3** [24, 25] involves intramolecular substitution of a fluorine atom in the aromatic ring by the carboxamide group formed *in situ* in the 1-aryl-2-cyanopyrroles **46** by the action of KOH. The formation of compounds **46** is a multistage process: Synthesis of the 1-arylpyrroles by the Clauson–Klaus reaction [11] and introduction of the CN group at position 2 of the pyrrole ring according to the scheme below.



45 **46** **48** **47** (80–94%)

R = H, F, CF_3

During the action of sodium hydride, substituted amides of pyrrolecarboxylic acids **49** undergo cyclization to 5-substituted pyrroloquinoxalin-4-ones **50** [26].

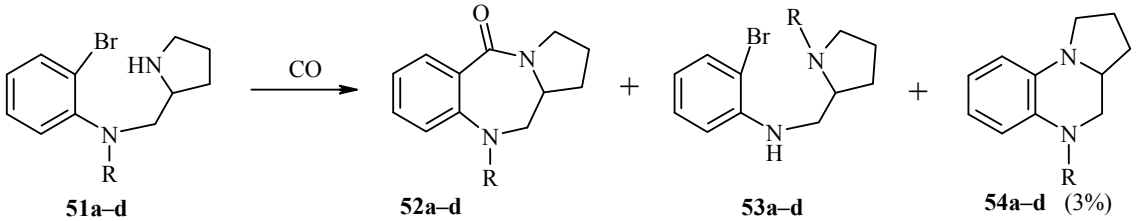


49a–f **50a–f** (45–84%)

49, 50 a R = Et, **b** R = C_6H_{11}, **c** R = Ph, **d** R = 2-$MeO_2CC_6H_4$, **e** R = 4-ClC_6H_4, **f** R = 4-$MeOC_6H_4$

Type A4 Production Methods

A special method for the synthesis of pyrrolo[1,2-*a*]quinoxalines using the **A4** synthon has not been developed. However, during the production of pyrrolo-1,4-benzodiazepines by the insertion of carbon monoxide into 2-[N-R-N-(2-bromophenyl)aminomethyl]pyrrolidines **51** in the presence of catalytic amounts of $Pd(OAc)_2$ and PPh_3 pyrrolo[1,2-*a*]quinoxalines **54** were found together with other products formed as a result of the migration of, for example, an acyl group from the aniline nitrogen atom to the pyrrolidine nitrogen atom [27].



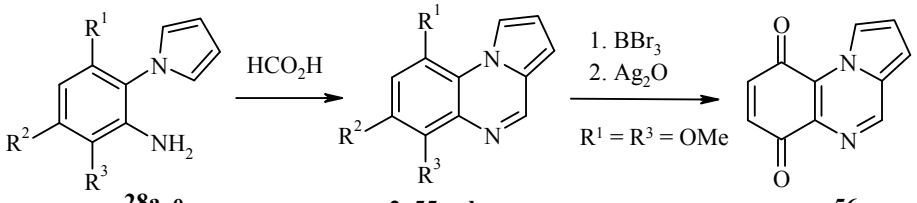
51a–d **52a–d** **53a–d** **54a–d** (3%)

51–54 a R = Ac, **b** R = CHO, **c** R = PhCO, **d** R = $MeSO_2$

The structure and the mechanism of formation of the pyrroloquinoxaline **54** in this reaction were partly clarified by realizing closure of the ring in compound **51** in an atmosphere of argon in the absence of carbon monoxide. Moreover, it was shown that heating of compound **51** in an atmosphere of argon in the absence of the palladium catalyst also leads to a small yield of the pyrrolo[1,2-*a*]quinoxalines. The part played by the catalyst in the closure of the pyrazine ring is not understood.

Type B1 Production Methods

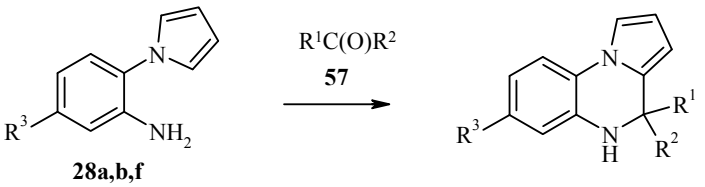
An excellent example illustrating the production of pyrroloquinoxalines by the **B1** path is the cyclization of 1-(2-aminophenyl)pyrroles with formic acid. Thus, boiling of compound **28a** in formic acid leads to the formation of unsubstituted pyrrolo[1,2-*a*]quinoxaline **2** with a yield of 80% [5, 28]. However, the reaction of the diaminophenylpyrrole **28e** under these conditions leads to the formation of 9-formyl-amidopyrroloquinoxaline **55d** [29].



2, 28 a $R^1 = R^2 = R^3 = H$; **28 b**, **c**, **55 a**, **b** $R^1 = R^3 = H$, **28b**, **55a** $R^2 = Me$, **28c**, **55b** $R^2 = Br$; **28d**, **55c** $R^1 = R^3 = OMe$, $R^2 = H$; **28e** $R^1 = NH_2$, $R^2 = R^3 = H$; **55d** $R^1 = NHC(O)H$, $R^2 = R^3 = H$

When an analogous strategy was used for the synthesis of pyrrolo[1,2-*a*]quinoxaline from 3,6-dimethoxy-2-nitroaniline, 6,9-dimethoxypyrrolo[1,2-*a*]quinoxaline (**55c**), interesting in view of the presence of the methoxy groups, was obtained; under the right conditions it was converted into 6,9-dihydroxypyrrolo[1,2-*a*] quinoxaline and pyrrolo[1,2-*a*]quinoxaline-6,9-dione (**56**). The heterocyclic quinone **56** can be used in the synthesis of more complex condensed systems by the Diels–Alder reaction with various dienes [30].

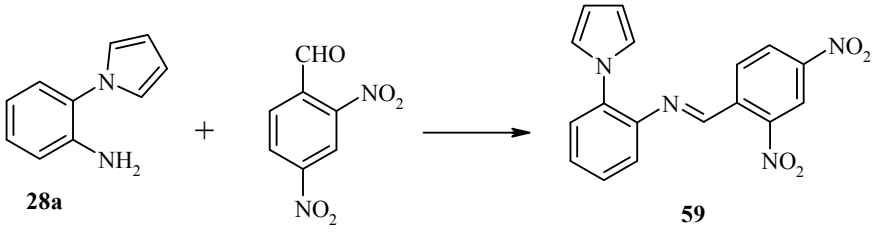
Methods for the synthesis of pyrrolo[1,2-*a*]quinoxalines based on 1-(2-aminophenyl)pyrroles began to develop after a more convenient and more effective method had been proposed for the production of the starting compound with an overall yield of 75%; this involved reduction of the 1-(2-nitrophenyl)pyrrole obtained from *o*-nitroaniline and 2,5-diethoxytetrahydrofuran. The yield of 1-(2-aminophenyl)pyrrole from *o*-phenylenediamine and tetrahydro-2,5-dipropoxyfuran amounts to only 40%, and isolation of the reaction product involves prolonged steam distillation. The availability of compounds **28** made it possible to develop convenient methods for the synthesis of pyrrolo[1,2-*a*]quinoxalines on the basis of reactions with compounds that are synthetic equivalents of a synthon of the $R^1R^2CH^{2+}$ type. 1-(2-Aminophenyl)pyrrole reacts with benz-, anis-, and veratraldehydes in boiling ethanol with the formation of 4,5-dihydro-4-phenylpyrrolo-[1,2-*a*]quinoxalines **58** with high yields [31]. The method was extended successfully to other aldehydes preferably containing electron-donating substituents and to cyclic ketones (cyclopentanone and cyclohexanone) and led to the production of pyrroloquinoxalines with yields from moderate to good depending on the nature of the carbonyl compound [31-33].



28a,b,f **58a–v** (31–96%)

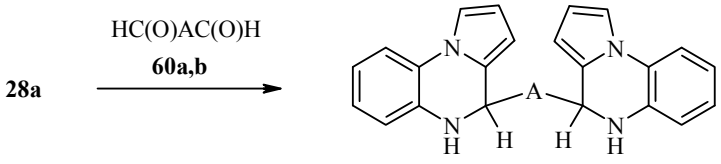
28 a R^3 = H, **b** R^3 = Me, **f** R^3 = OMe; **58 a–s** $R^2 = R^3$ = H, **a** R^1 = Ph, **b** R^1 = 4-$MeOC_6H_4$, **c** R^1 = 3,4-$(MeO)_2C_6H_3$, **d** R^1 = 4-$CF_3OC_6H_4$, **e** R^1 = 2,3-$(HO)_2C_6H_3$, **f** R^1 = 3,4,5-$(MeO)_3C_6H_2$, **g** R^1 = 3,5-Cl_2-2-$(HO)C_6H_2$, **h** R^1 = CF_3, **i** R^1 = 3-Py, **j** R^1 = 3-hromyl, **k** R^1 = stiryl, **l** R^1 = *i*-Bu, **m** R^1 = $C_{11}H_{23}$, **n** R^1 =H, **o** R^1 = Me, **p** R^1 = Et, **q** R^1 = $CMe_2(CH_2)_2CN$, **r** R^1 = 2-HOC_6H_4, **s** R^1 = 3-$MeOC_6H_4$; **t** R^1= Me, R^2 = CO_2Et; R^3 = H; **u** R^1 = H, R^2 = Ph, R^3 = Me; **v** R^1 = H, R^2 = Ph, R^3 = OMe

In spite of the fact that 1-(2-aminophenyl)pyrrole is consider an excellent reagent in the synthesis of 4-substituted 4,5-dihydropyrrolo[1,2-*a*]quinoxalines the possibility of using it depends largely on the nature of the carbonyl compound and the reaction conditions. The formation of 4,5-dihydropyrrolo[1,2-*a*]quinoxalines according to the schemes described above involves a reaction of the Mannich type, which requires a primary or secondary amine, an aldehyde (mostly formaldehyde), and a nucleophilic carbon atom. As a rule the use of other active aldehydes in place of formaldehyde in the Mannich reaction sometimes does not lead to the desired results [34, 35]. For this reason the authors of [36] attempted to extend the limits of the synthesis of pyrrolo[1,2-*a*]quinoxalines by using 1-(2-aminophenyl)pyrrole, which contains an amino group and a nucleophilic carbon atom at the same time. It was found that heating of a solution of compound **28** and the aldehydes **57** at 50°C in ethanol in the presence of a catalytic amount of acetic acid led to 4,5-dihydro-pyrrolo[1,2-*a*]quinoxalines **58** with yields of 70-96% irrespective of the nature of the employed aldehyde [36]. If aliphatic aldehydes such as isobutanal or undecanal are used the formed 4,5-dihydropyrrolo[1,2-*a*]quin-oxalines are gradually oxidized to pyrroloquinoxalines, and they were therefore characterized in the form of the N(5)-acyl derivatives. The mild conditions of the reaction (50°C, a catalytic amount of acetic acid) guarantee widespread use of this method, although it is necessary to point out that 2,4-dinitrobenzaldehyde did not give the cyclization products under any conditions. The reaction resulted in the formation of Schiff's bases of type **59** even under very rigorous conditions.



28a **59**

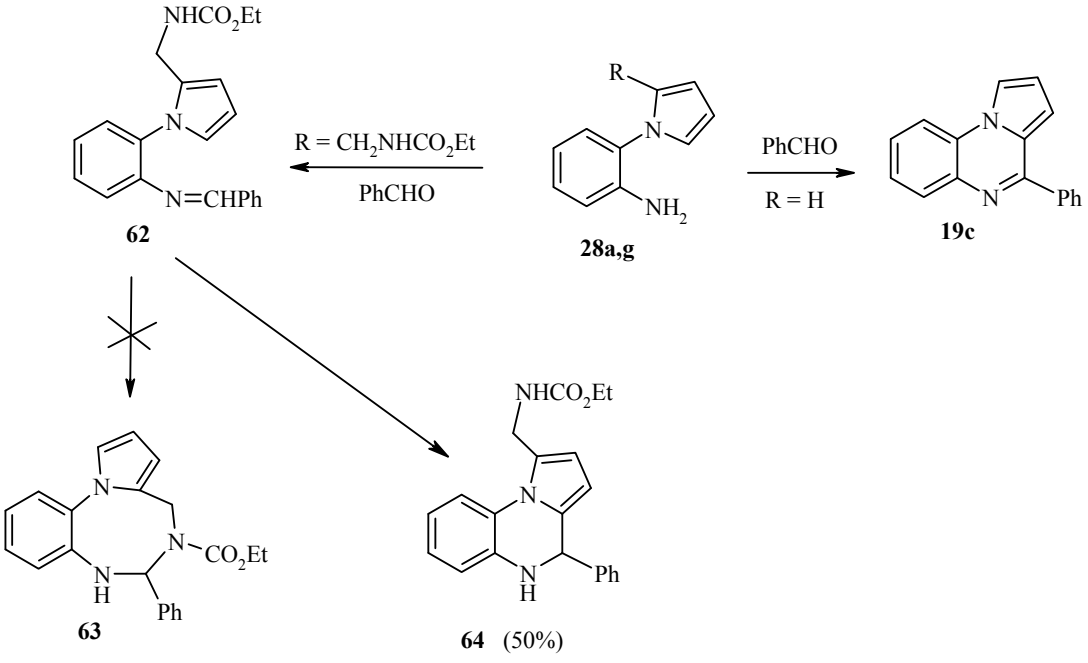
The reaction of the bisaldehydes **60** with 2-aminophenylpyrrole **28a** leads to bispyrroloquinoxalines **61** [32].



61a,b (32–65%)

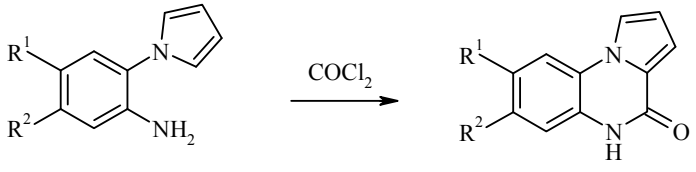
60, 61 a A = $(CH_2)_5$, **b** A = $(CH_2)_6$

Cyclization in a basic medium also takes place in the case of the reaction of benzaldehyde with derivative of 1-(2-aminophenyl)pyrrole. For example, treatment of the aminoester **28g** with an equimolar amount of benzaldehyde in pyridine gives 4,5-dihydropyrrolo[1,2-*a*]quinoxaline **64** and not the expected pyrrolobenzotriazocine **63** [37]. The postulated intermediate in this reaction is probably the imine **62**. The reaction of compound **28a** with benzaldehyde in the presence of copper acetate leads to 4-phenylpyrroloquinoxaline **19c**.



28 a R = H, **g** R = CH_2NHCO_2Et

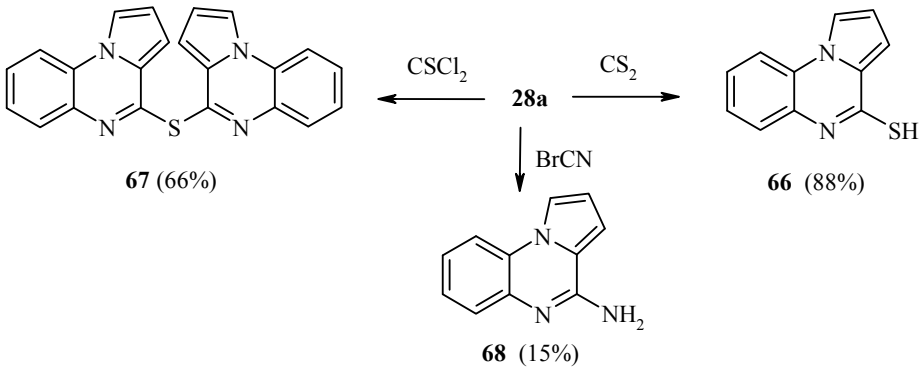
If phosgene or triphosgene is used as synthetic equivalent of the synthon R_2C^{2+} during construction of the pyrroloquinoxaline system from derivatives of 1-(2-aminophenyl)pyrrole 4,5-dihydropyrrolo[1,2-*a*]quinoxalin-4-ones **65** with a highly reactive carbamoyl function are formed. Syntheses of a series of functionally substituted derivatives of pyrrolo[1,2-*a*]quinoxalines **65** of pharmacological interest by this method have been described [8, 10, 38-45].



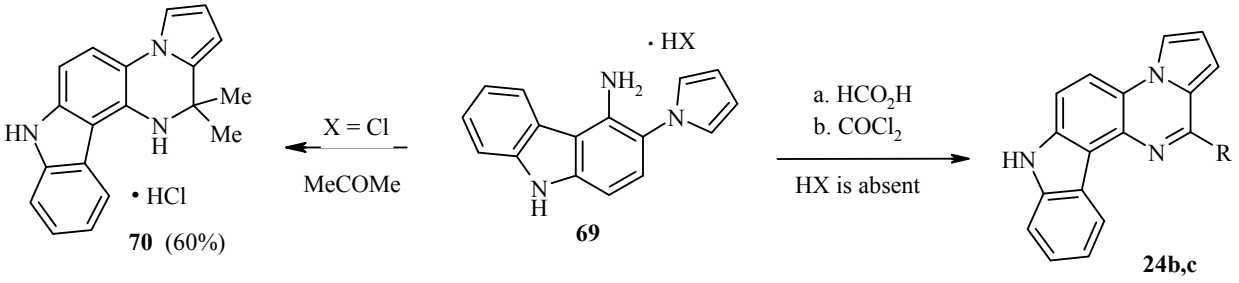
65a–j (53–100%)

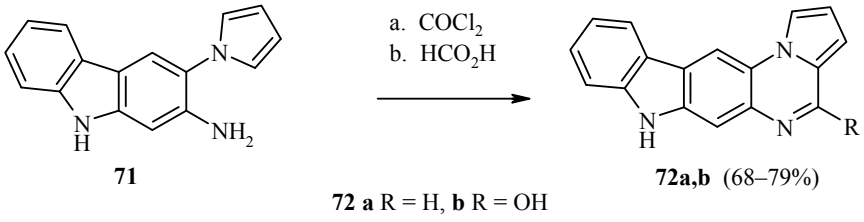
a–f R^1 = H, **a** R^2 = Cl, **b** R^2 = H, **c** R^2 = OMe, **d** R^2 = Me, **e** R^2 = CN, **f** R^2 = BnO;
g R^1 = Cl, R^2 = H, **h** R^1 = R^2 = Cl; **i** R^1 = OMe, R^2 = H; **j** R^1 = R^2 = Me

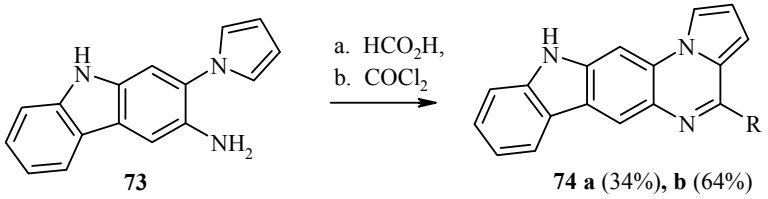
The reaction of aminophenylpyrrole **28a** with carbon disulfide in the presence of sodium hydroxide and with thiophosgene leads to 4-mercaptopyrroloquinoxaline (**66**) and to the sulfide **67** respectively [8, 43], while reaction with BrCN in the presence of sodium carbonate leads to the formation of 4-aminopyrroloquinoxaline **68** [8].



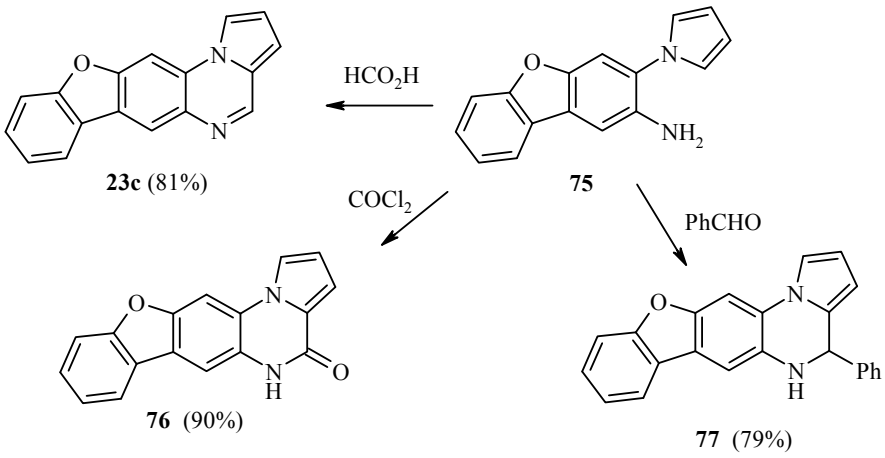
By extending the above-described method for the construction of the pyrrolo[1,2-*a*]quinoxaline system based on 1-(2-aminophenyl)pyrroles [11] to condensed heterocyclic systems containing vicinal amino groups in the benzene fragment it is possible to synthesize polycondensed heterocyclic systems with pyrrolo[1,2-*a*]quinoxaline structural fragments. For example, it was shown that three different pentacyclic condensed heterocyclic systems – derivatives of pyrrolopyrazinocarbazoles **24**, **72**, and **74** are formed, depending on the nature of the source of the one-carbon fragment and the method of cyclization of the 4-amino-3-(pyrrol-1-yl)carbazole (**69**) and its isomeric 2-amino-3-(pyrrol-1-yl)- (**71**) and 3-amino-2-(pyrrol-1-yl)carbazoles (**73**) [12-14, 46].



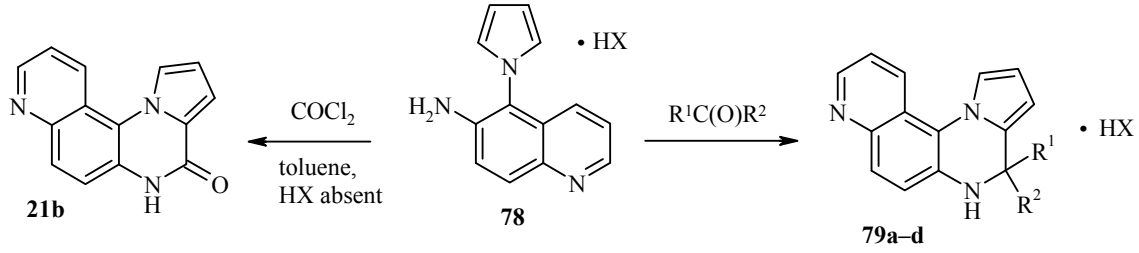




When the same authors used the analogous strategy, functional derivatives of benzofuro[3,2-*g*]-pyrrolo[1,2-*a*]quinoxalines **23c**, **76**, and **77** were synthesized [13] based on 2-amino-3-(pyrrol-1-yl)dibenzofuran (**75**).

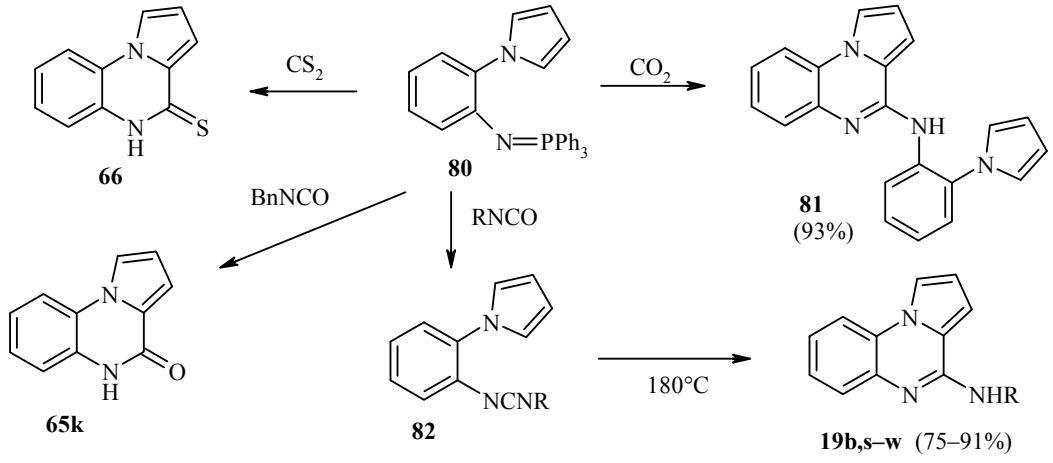


In a similar way the authors of [12] synthesized pyrido[2,3-*h*]pyrrolo[1,2-*a*]quinoxalines **79** and **21b** from the hydrohalide of 6-amino-5-(pyrrol-1-yl)quinoline (**78**). The reactions of the 6-amino derivative **78** with anisaldehyde and acetone under normal conditions and with pyruvic acid and with benzyl methyl ketone under the conditions of a Mannich condensation gave the corresponding 4,5-dihydro derivatives of pyrido[2,3-*h*]-pyrrolo[1,2-*a*]quinoxalines **79** [12].



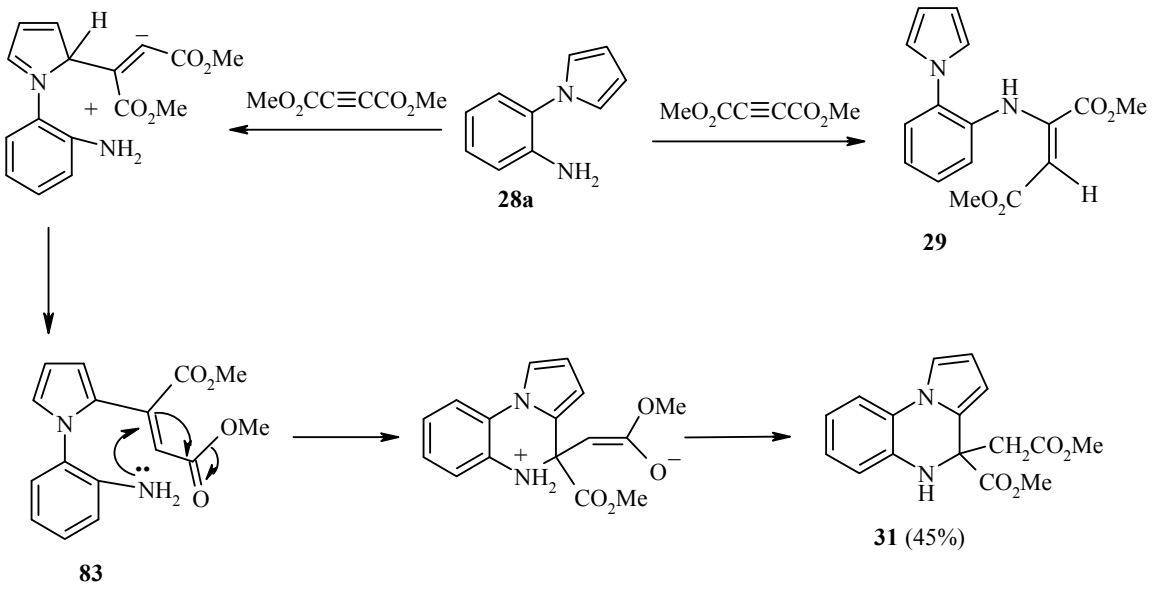
79 a R^1 = H, R^2 = 4-$MeOC_6H_4$, HX absent, **b** R^1 = R^2 = Me, X = Cl,
c R^1 = Me, R^2 = CO_2H, X = Cl, **d** R^1 = Me, R^2 = CH_2Ph, X = Br

Various heterocumulenes can be used as synthetic equivalents of the RC^{3+} synthon. In reaction with isocyanates, isothiocyanates, carbon dioxide, or carbon disulfide by the Wittig reaction the iminophosphates **80**, obtained from *o*-(1-pyrrolyl)phenyl azide, form *o*-pyrrolylphenylheterocumulenes, which undergo cyclization to condensed pyrroloquinoxalines **19**, **65k** (R^1 = R^2 = R^3 = H), **66**, and **81** [47, 48].

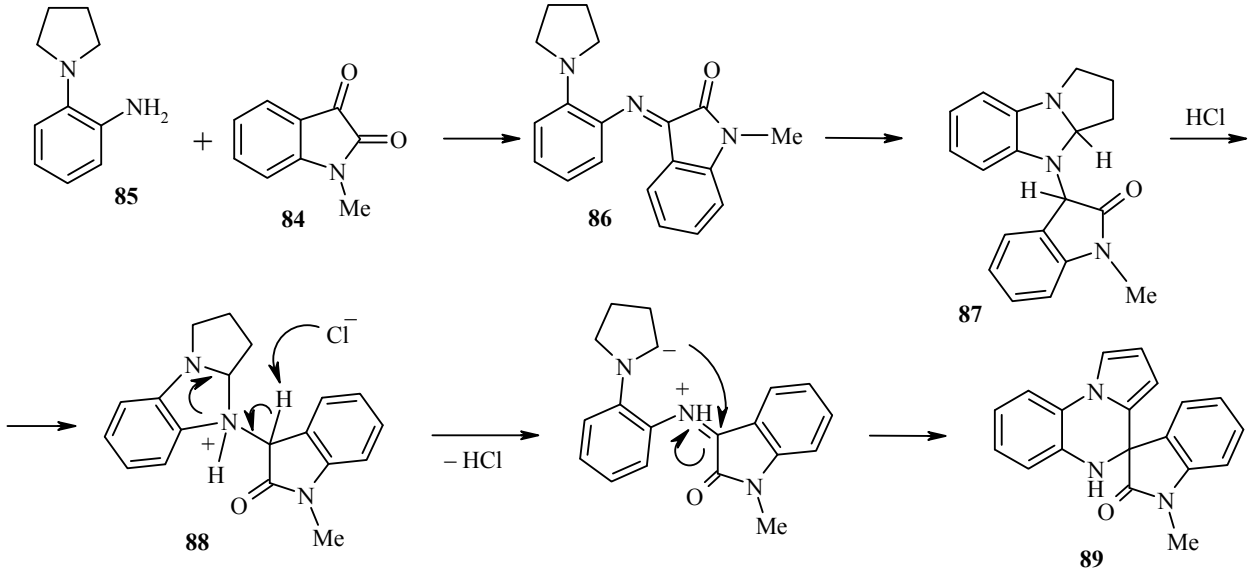


19 b R = Ph, **s** R = 2-Pr, **t** R = 4-ClC_6H_4, **u** R = 3-MeC_6H_4, **v** R = 4-MeC_6H_4, **w** R = 4-$MeOC_6H_4$

The reaction of 1-(2-aminophenyl)pyrrole (**28a**) with dimethyl acetylenedicarboxylate, which acts as provider of the one-carbon fragment in the construction of the pyrrolo[1,2-*a*]quinoxaline system, takes place in chloroform for 36 h with the formation of the pyrroloquinoxaline **31** (yield 45%) and dimethyl 2-(pyrrol-1-yl)-anilinofumarate (**29**) (yield 40%). Compound **31** could be formed from dimethyl fumarate as a result of an intramolecular ene cyclization. In fact, such a transformation was observed, but before completion it required boiling of compound **29** in chloroform for a week. However, it should be noted that an amount of compound **31** detectable by spectral methods is formed after brief heating of the reaction mixture. It is not, therefore, impossible that part of compound **31** is formed according to the scheme presented below [15].



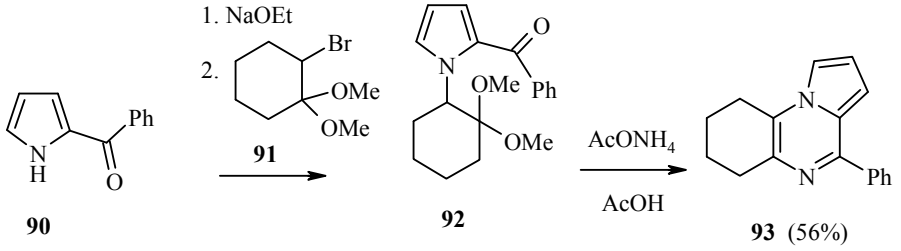
N-Methylisatin (**84**) can also be used as a one-carbon fragment that reacts with 1-(2-aminophenyl)-tetrahydropyrrole (**85**) in ethanol in the presence of conc. HCl with closure of the pyrazine ring according to the scheme presented below [49].



It was shown experimentally that whereas the first two stages of the reaction (the formation of the Schiff's base **86** and the benzimidazole derivative **87**) can take place in the absence of hydrochloric acid the presence of the acid is necessary for enlargement of the imidazole ring to a pyrazine ring according to a scheme analogous with the Stevens rearrangement.

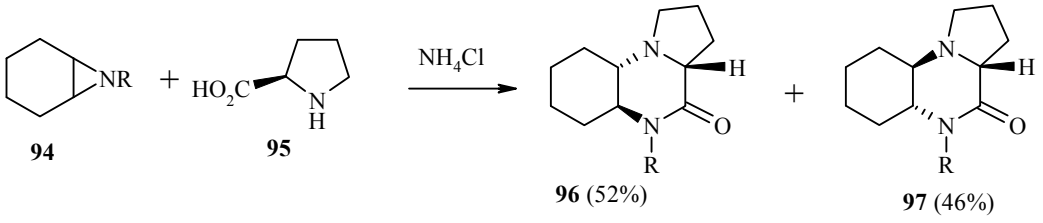
Type B2 Production Methods

During realization of the approach corresponding to the retrosynthetic path **B2**, in contrast to all the above-mentioned methods for the synthesis of pyrrolo[1,2-*a*]quinoxalines where closure of the pyrazine ring takes place as a result of intramolecular cyclization, the concluding stage of the formation of the ring involves the participation of two reagents, i.e., it is intermolecular. The proposed method for the synthesis of pyrrolo[1,2-*a*]quinoxaline according to the **B2** path involves alkylation of the sodium derivative of 2-benzoyl-pyrrole (**90**) by the dimethyl ketal of α-bromocyclohexanone (**91**) followed by treatment of the reaction product with ammonium acetate in acetic acid. Here it should be noted that only one compound, 4-phenylpyrrolo[1,2-*a*]-quinoxaline **93** was synthesized by this method [50].

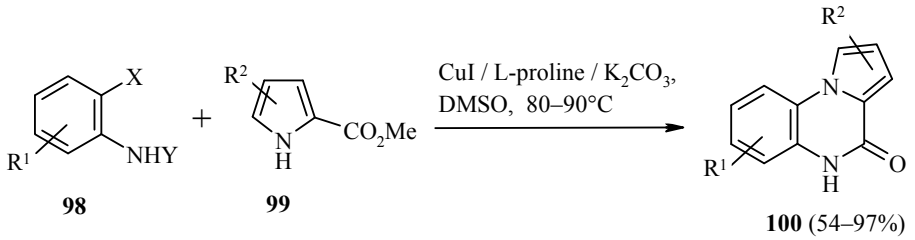


Type D Production Methods

In reaction with derivatives of α-amino acids (glycine, L-alanine, L-phenylalanine, and L-proline) with opening of the aziridine ring and spontaneous closure of the piperazine ring condensed aziridines of type **94** lead to optically active representatives of new *trans*-bicycloperhydro-2(1H)-quinoxalines and tricycloperhydro-pyrrolo[1,2-*a*]quinoxalin-4(4H)-ones **96** and **97** (in the case of proline), the production of which represents realization of the retrosynthetic approach **D** [51].



In [52] an effective one-pot method was proposed for the synthesis of pyrroloquinoxalines based on the condensation of *o*-aminoiodobenzene and its derivatives **98** with methoxycarbonylpyrroles **99** catalyzed by copper iodide and L-proline in the presence of potassium carbonate.



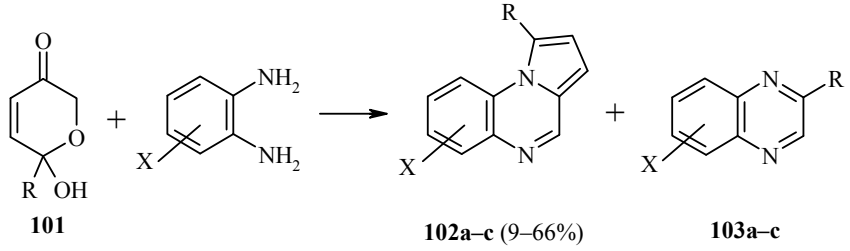
98 X = I, Br; Y = H, $COCF_3$; **98**, **100** R^1 = H, OMe, Me, F, Ac
99, **100** R^2 = H, Et, Cl, Ac, CO_2Me

Other Methods of Synthesis

By such methods for the synthesis of pyrrolo[1,2-*a*]quinoxalines we have in mind methods based either on condensed derivatives of pyrroles (a) either on compounds not containing a pyrrole ring or a quinoxaline system (b). During realization of approach (b) the pyrroloquinoxaline system can be produced through the initial formation of the quinoxaline system (b-*I*) or of the pyrrole ring (b-*II*). In this review we only discuss the second version (b-*II*).

A typical example is the transformation of 4-(indolin-3-yl)pyrrolidinobenzimidazole **87** to the spiro derivative of pyrrolidinoquinoxaline **89** by the action of hydrochloric acid in the Stevens rearrangement, as shown above [49].

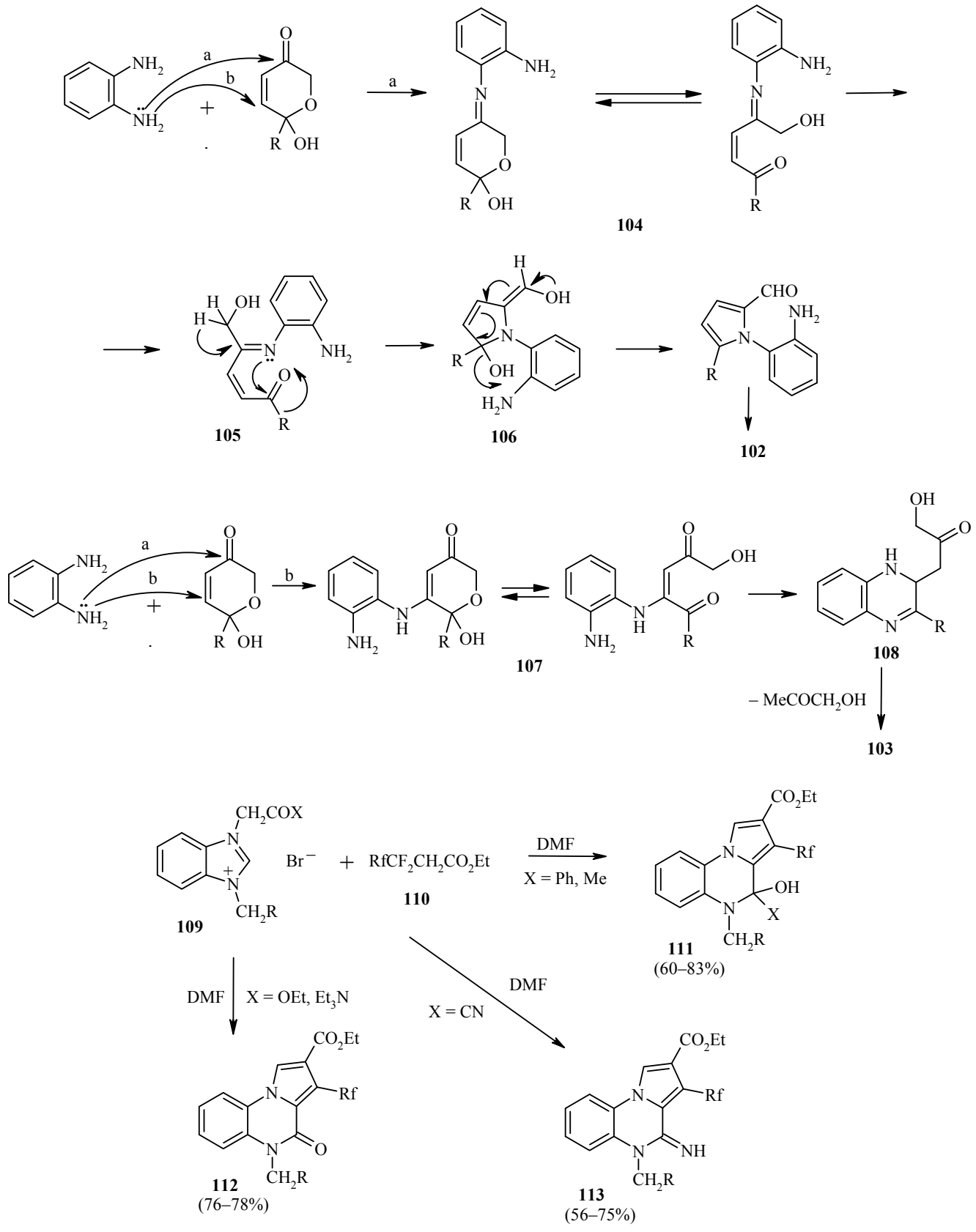
Boiling of 6-hydroxy-6-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2H-pyran-3-one (**101**) (obtained by the oxidation of 2-hydroxymethyl-5-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)furan with *m*-chloroperbenzoic acid [53] or pyrazinium chlorochromate [54]), and *o*-phenylenediamine for 2 h in chloroform gives a 43% yield of the quinoxaline derivative **103** and a 16% yield of the pyrrolo[1,2-*a*]quinoxaline derivative **102**; a plausible mechanism for the formation of the latter probably involves nucleophilic attack by the *o*-phenylenediamine at the carbonyl group of the pyran ring in compound **101** followed by the formation of the Schiff's base **104**, which opens under the reaction conditions, giving the imino ketone **105**. Compound **105** undergoes cyclization to the enolic form **106** and is converted, after dehydration, into the tricycle **102** (path a). Compound **103** is probably formed by path b through addition of the *o*-phenylenediamine to compound **101** in a reaction of the Michael type and ring opening, leading to the diketodiamine **107**. Compound **107** undergoes cyclization and gives the dihydroquinoxaline **108**, which forms compound **103** after the loss of dihydroxyacetone [55].



101–103 R = 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl;
102, **103 a** X = H, **b** X = NO_2, **c** X = Cl

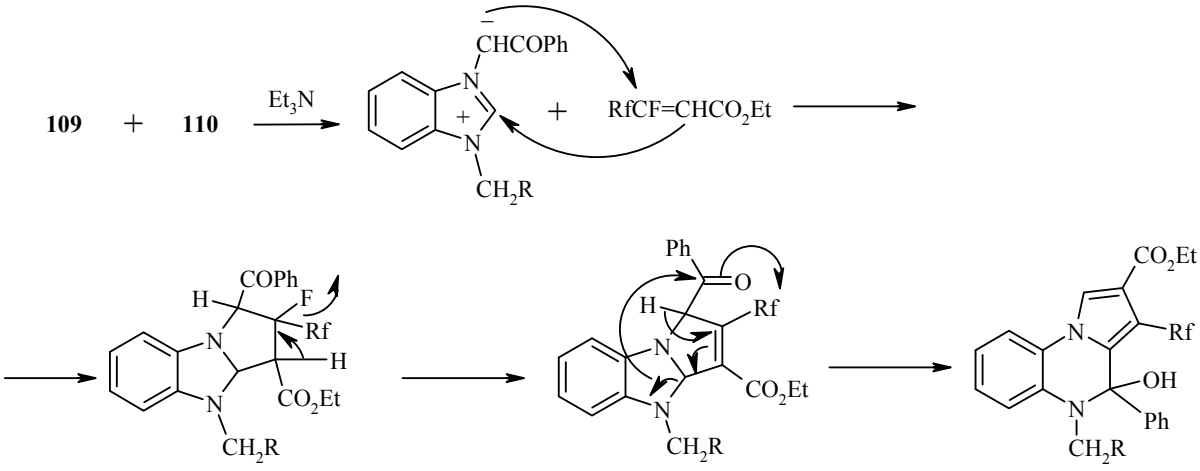
If derivatives of *o*-phenylenediamine are used in this reaction isomers differing in the substituents at positions 6 and 7 in the case of compounds of type **103** and at positions 7 and 8 in the case of compounds of type **102** are formed [56].

During the action of polyfluoroalkanoates **110** in the presence of bases the benzimidazole derivatives **109** rearrange, giving good yields of the 4-substituted pyrrolo[1,2-*a*]quinoxalines **111-113** [57, 58].

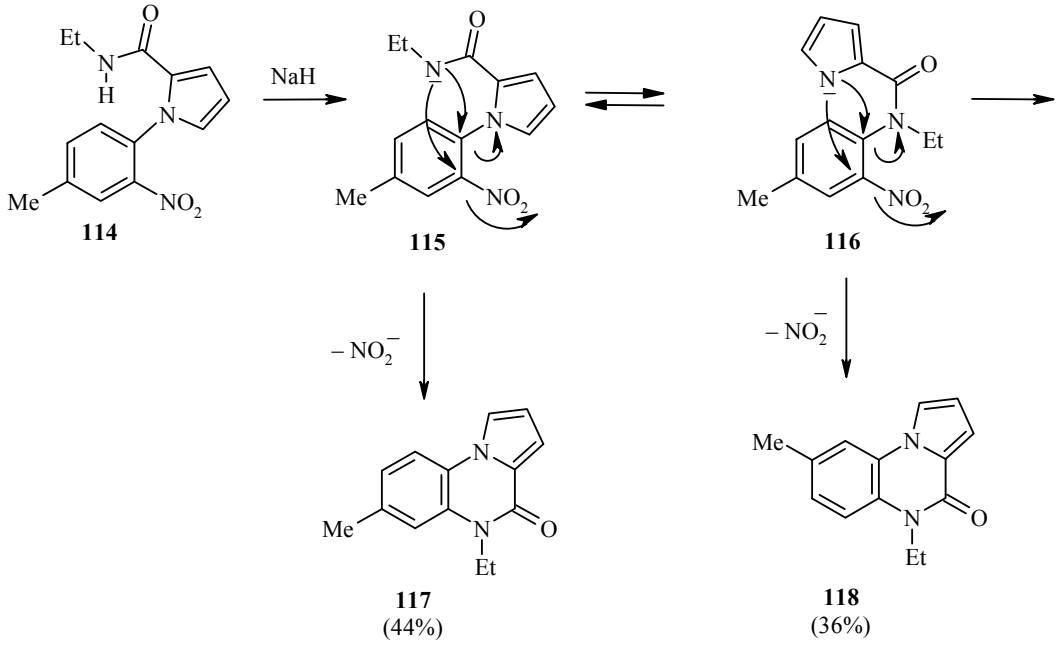


R = H, Ph; Rf = HCF_2, $ClCF_2$, CF_3, $Cl(CF_2)_3$, $Cl(CF_2)_5$, $Cl(CF_2)_7$, $F(CF_2)_7$

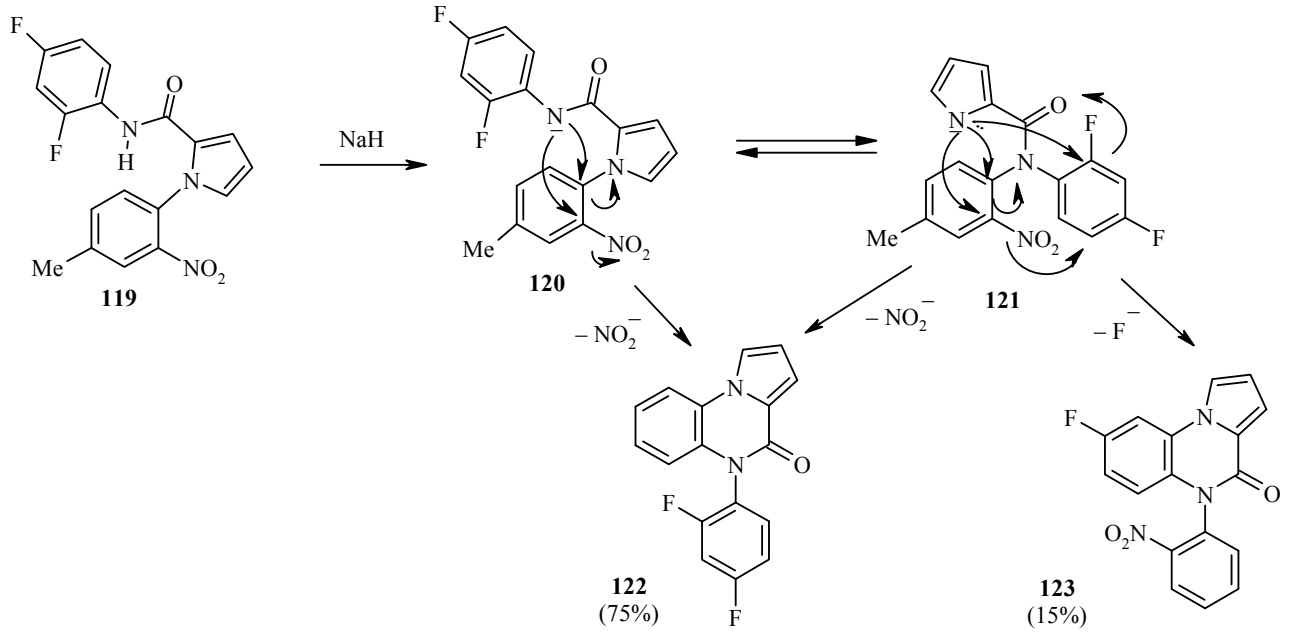
In the opinion of the authors of [57, 58] the pyrroloquinoxaline system is formed from the benzimidazole system according to the scheme presented below.



As already discussed above, the substituted amides of pyrrolecarboxylic acids **49** undergo cyclization with sodium hydride to substituted pyrroloquinoxaline-4-ones **50** [26]. However, together with the usual *ipso* substitution of the nitro group, leading to the formation of pyrroloquinoxalines **117**, the anion **115** undergoes a Smiles rearrangement to the anion **116**, the further cyclization of which leads to the formation of the pyrroloquinoxaline **118** [26].



If there is an *o*-fluorine-substituted phenyl group in the amide fragment, attack by the rearranged anion **121** leads both to cyclization with substitution of the nitro group in one of the aryl fragments and the formation of the pyrroloquinoxaline **122** and to substitution of the fluorine atom in other aryl group and the formation of pyrroloquinoxaline **123** [26].



CONCLUSION

TABLE 1. Probable and Implemented Methods for the Synthesis of Pyrrolo[1,2-*a*]quinoxalines Based on Phenylpyrrole Derivatives

Based on phenylpyrroles	
Probable	Implemented (number of papers)
A1, **A2**, **A3**, **A4**	**A1** (12), **A2** (8), **A3** (2), **A4** (1)
B1, **B2**	**B1** (28), **B2** (1)
C1, **C2**	**C1** (0), **C2** (0)
D	**D** (2)
E	**E** (0)

According to the data in the table, of the ten possible methods for the synthesis of pyrrolo[1,2-*a*]quinoxalines the most successful are the methods based on the **A1** and **B1** approaches, while as shown above the methods based on the **C1**, **C2**, and **E** approaches can only be realized when effective methods have been developed for the C–N coupling of benzene derivatives, amines, and pyrroles, making it possible to synthesize the required structural units for the production of pyrrolo[1,2-*a*]quinoxalines depending on the required objective.

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