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FORMAZANS IN THE SYNTHESIS OF HETEROCYCLES. II.* SYNTHESIS OF AZINES (REVIEW)

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The review is devoted to the use of formazans in the synthesis of azines.

Keywords: annelated 1,2,4-triazines, azines, benzo-1,2,4-triazine, bora-2,3,5,6-tetrazine, 1,4-dihydro-1,2,4,5-tetrazine, 1,6-dihydro-1,2,4,5-tetrazine, formazans, 1,2,3,4-tetrahydro-1,2,4,5-tetrazine, 1,2,4,5-tetrazine, 1,3,4-thiadiazine, 1,2,4-triazine, verdazyls.

The availability of various types of formazans, the prospects for their use in the synthesis of heterocycles, and the principles of the construction of various heterocyclic systems on the basis of the formazan fragment have already been discussed in general features in the first part of our review devoted to the synthesis of azoles on the formazans basis [1]. We will therefore only present a more detailed scheme of the possible paths to the formation of six-membered heterocyclic systems from formazans. As in the case of azoles, the principles of the construction of azine rings are based on the ability of the formazan fragment to enter completely or partially into the heterocycle that forms (Scheme 1) [2-11]. Most of the described paths (*a*-*g* in Scheme 1) involve intramolecular cyclization quite often without isolation of the precursor. There are only two examples of intermolecular [4+2] cycloaddition of formazans as 1,2,4-triazabuta-1,3-dienes with only one type of dienophile (path *h*) [12], since it has been demonstrated that the formation of 1,4-diaryl-3,6-bis(arylazo)-1,4-dihydro-1,2,4,5-tetrazines from 1,5-diaryl-3-chloroformazans (path *i*) is a two-step process and can be regarded as a variant of the intramolecular cyclization of path *d* (Scheme 1).

The N-1 atom and one of the atoms of the substituents at the N-5 atom of the formazan fragment are most often involved in the intramolecular cyclization of formazans to azine derivatives according to a [6+0] scheme (paths *a*-*c*, described for the C and B atoms). In other cases the formation of the six-membered ring according to the [6+0] scheme results from nucleophilic substitution by a fragment of the *meso* substituent (from R^3) at the N-5 atom of the formazan fragment (paths *d*-*f* and, possibly, *i*). The cyclization of formazans with loss of one of the nitrogen atoms has only been described for cases of the formation of benzo-1,2,4-tria-zines (path *h*) [2-5, 10, 11].

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* For Communication 1, see [1].

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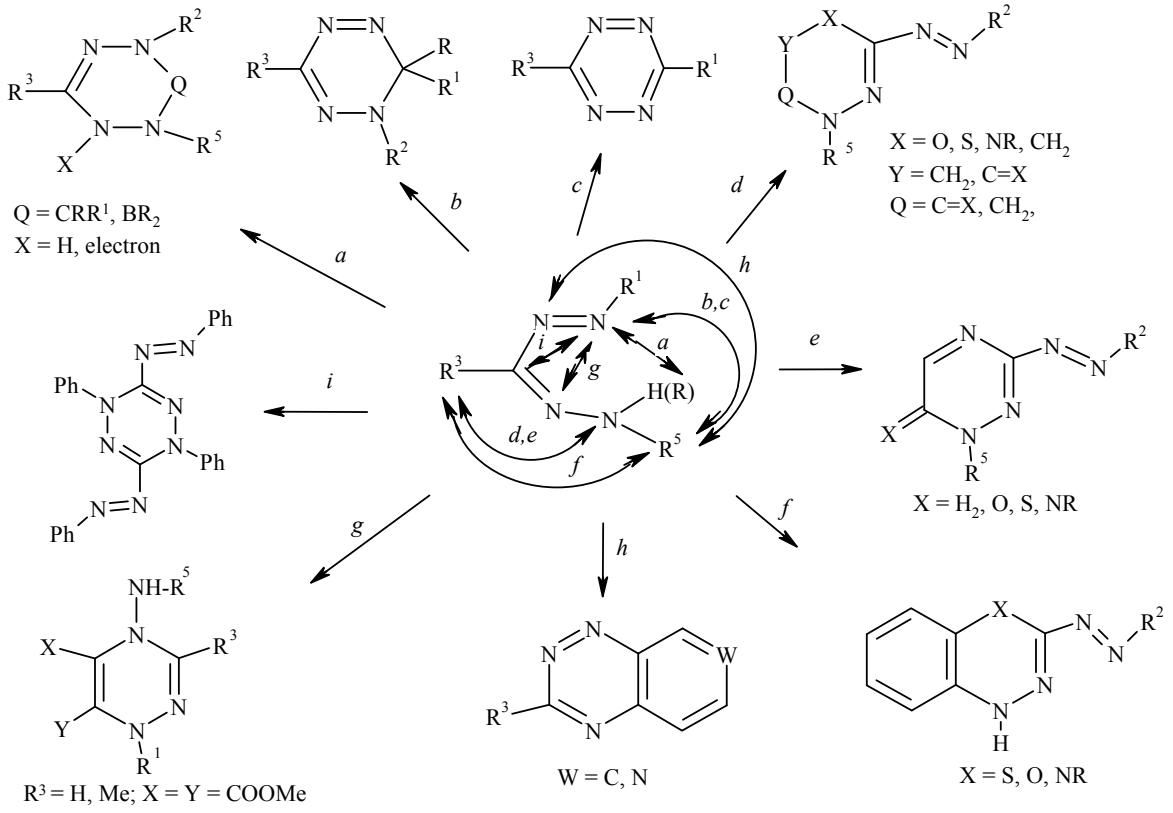
Scheme 1



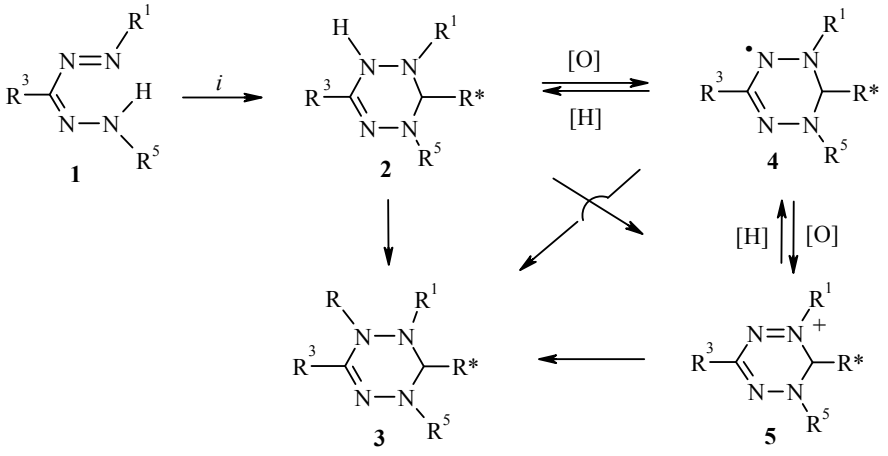
The degree to which the paths for the production of azines from formazans have been studied is extremely varied. For example, syntheses of derivatives of tetrahydro-1,2,4,5-tetrazines (verdazyls, etc.) have been studied so well that many reviews and books have been devoted to them [2-4, 7], and their description has been included in students' workshop [13]. The method for the synthesis of benzo-1,2,4-triazines from formazans [2-5, 10, 11] is very extremely popular and competitive. Syntheses of other azines (1,3,4-thiadiazines and their benzo analogs) are represented by isolated examples (path *c-f*) or have not yet been achieved (1,3,4-oxadiazines and their benzo analogs) or lead to poorly stable systems (path *b*) [2-4, 14]. On the whole the synthetic potential of the described and potential reactions for the synthesis of azines from formazans has clearly been undervalued.

1. DERIVATIVES OF 1,2,4,5-TETRAZINE

1.1. 1,2,3,4-Tetrahydro-1,2,4,5-tetrazines

Formazans **1** occupy a very important position as precursors in the synthesis of well studied 1-H- (leucoverdazyls **2**) and 1-R-1,2,3,4-tetrahydro-1,2,4,5-tetrazines **3**, verdazyl free radicals **4**, and verdazyl cations **5** (Scheme 2) [3-8, 15, 16]. The chemistry of these types of 1,2,3,4-tetrahydro-1,2,4,5-tetrazines is closely related (Scheme 2) [3, 4, 7, 17]. They are all produced by path *a* in Scheme 1 in that the N–C bond involving the N-1 nitrogen atom and the carbon atom of the second substituent at the N-5 atom is formed during the cyclization process. This substituent, e.g., an alkyl group, is either present in the precursor or is introduced during the reaction.

Scheme 2



R^1, R^5 = Ar; R^3 = H, Ar, Alk, Het, 3-Py, 4-Py, 2-Py, CN, COOR, AlkS, AlkO, RSO_2; Bn, CMe_3, acyl, C(O)NHR, sugar fragments; R* = H, Alk, OH, $NAlk_2$; $N(CH_2CH_2)_2CH_2$, $N(CH_2CH_2)_2O$, 1,2,3,4-tetrahydroisoquinolino; *i* = MeI, $PhCH_2Br$, benzotriazinylCH_2R*, CH_2O, CH_2O+HNR_2

The accessibility of the initial formazans and the high stability of the verdazyl radicals have attracted and are still attracting the attention of chemists, biologists, and physicists [2-14, 18-33]. New verdazyls [15-17, 19, 33] and their complexes with metals [16, 21-25, 27, 28, 30] and with π-acceptors [26, 29, 31, 32] are regularly being synthesized, new characteristics of known verdazyls are being studied, and new aspects of their application are being sought, as in the creation of linear and helical polymers, organic magnetic materials, semiconductors, luminophores, etc. [20, 21, 25, 27, 30]. The verdazyls **4** are reduced reversibly to leucoverdazyls **2** and are oxidized to verdazyl cations **5** and form complexes with benzene, benzoquinones, and other *n*- and π-acceptors [2-4, 7, 26, 29-33], making it possible to use them for the solution of many problems of organic chemistry, including the study of one-electron transfer processes. The verdazyl method (the Dvorko method) has been used successfully to study the kinetics and mechanisms of the monomolecular heterolysis of organohalogen compounds, including industrially employed compounds [7, 34, 35], although the principles of the method have undergone revision [36].

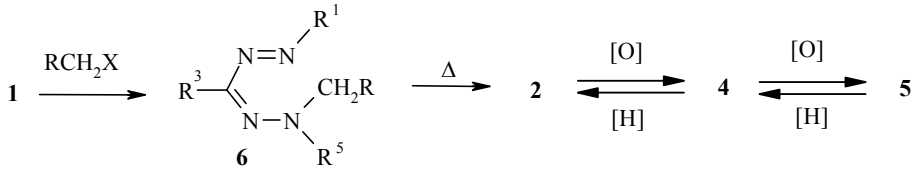
In spite of the fact that the "verdazyl–leucoverdazyl" and "verdazyl–verdazyl cation" systems are similar in spectral and color characteristics to the "formazan–tetrazolium salt" system they have not been used so widely as the latter in biology, although attempts have been made. For this purpose water-soluble verdazyls containing sugar residues at position 3 or sulfo groups in the aryl fragments were synthesized [7, 37].

Formazans were first converted into verdazyls for the production of stable radicals. Considerable attention was then paid to the effect of the nature of the substituents on the respective reactions and to attempts at the synthesis of compounds with two, three, and four formazan groups in order to produce polyverdazyls, including polymers with verdazyl side fragments. At the center of attention during study of the properties of verdazyls were the syntheses of leucoverdazyls **2**, their N(1)-substituted derivatives **3**, and verdazyl cations **5** and the properties of various representatives of these three groups of 1,2,3,4-tetrahydro-1,2,4,5-tetrazines (Scheme 2) [2-12]. Greater attention had to be paid to the initial 5-alkyl-1,5-diaryl-3-R-formazans. Many 1-H-1,2,3,4-tetrahydro-1,2,4,5-tetrazines **2** have found use in organic chemistry as subjects for study of the inversion of the heterocycle, the annular tautomerism, and the determination of the strength of the N–H bond in the tetrahydrotetrazine ring. 4-(Tetrazolyl)leucoverdazyls were found to be strong antioxidants [7].

5-Alkyl-1,5-diaryl-3-R-formazans **6** are the main precursors in the synthesis of derivatives of 1,2,3,4-tetrahydro-1,2,4,5-tetrazine **2**-**5** (Scheme 3). Until now 5-alkylformazans **6** have only been obtained by the

alkylation of formazans. Methyl iodide and alkyl bromides, and more rarely other haloalkanes or dimethyl sulfate, are most often used for these purposes [4, 7, 17]. As in the alkylation of representatives of other groups of hydrazones, in these cases base catalysis is required, and the reaction takes place with the participation of formazanthiones [2-4, 7, 17]. Depending on the conditions of alkylation of the formazans **1**, the leucoverdazyls **2**, verdazyls **4**, or verdazyl cations **5** can be obtained straight away instead of the 4-alkylformazans **6**. All the versions of the production of 1,2,4,5-tetrazine derivatives are used in practise, although the mechanism of the cyclization of 5-alkylformazans has not yet been discussed.

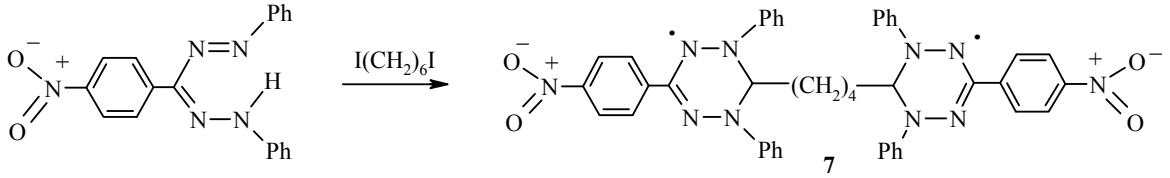
Scheme 3



R = H, C_nH_{2n-1}, n = 1–14

In the reactions of the formazans **1** with methylene diiodide, as also with methyl iodide or bromoalkanes, only the monoverdazyls **4** are formed; with hexamethylene diiodide the diverdazyl **7** was obtained.

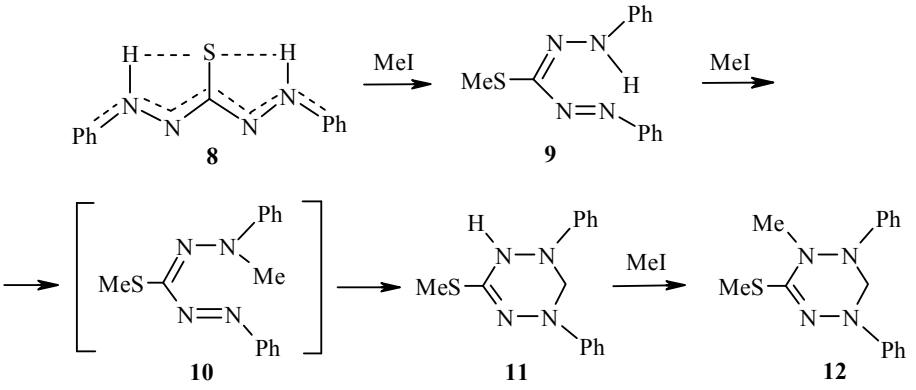
Scheme 4



In solutions 1,5-diaryl-3-R-formazans, which have substituents similar in electronic characteristics at positions 1 and 5, exist in two tautomeric forms [2-4]. During the alkylation of such formazans two isomeric 5-alkyl-1,5-diarylformazans are formed, but they are both transformed into one leucoverdazyl [4, 7].

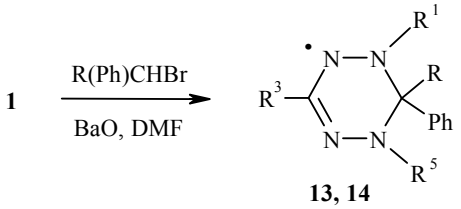
It is not possible to stop the alkylation of the dithizone **8** or the 3-alkylsulfanyl-1,5-diphenylformazans **9** at the stage of the 5-alkyl derivatives **10** (Scheme 5). From the reaction mixture here it is possible to isolate the leucoverdazyl **11** and to alkylate it further to the 1-alkyl-6-alkylsulfanyl-2,4-diphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine **12** [4, 37].

Scheme 5



The alkyl halides can have a long (up to $C_{15}H_{31}$) or a branched chain and aryl or hetaryl substituents [2-4, 17]. Thus, if benzyl bromide is used tetraphenylverdazyls **13** are obtained from the formazans **1**, and if benzhydrol bromide is used pentaphenylverdazyl **14** is obtained (Scheme 6).

Scheme 6



13, 14

13 R = H, **14** R = Ph

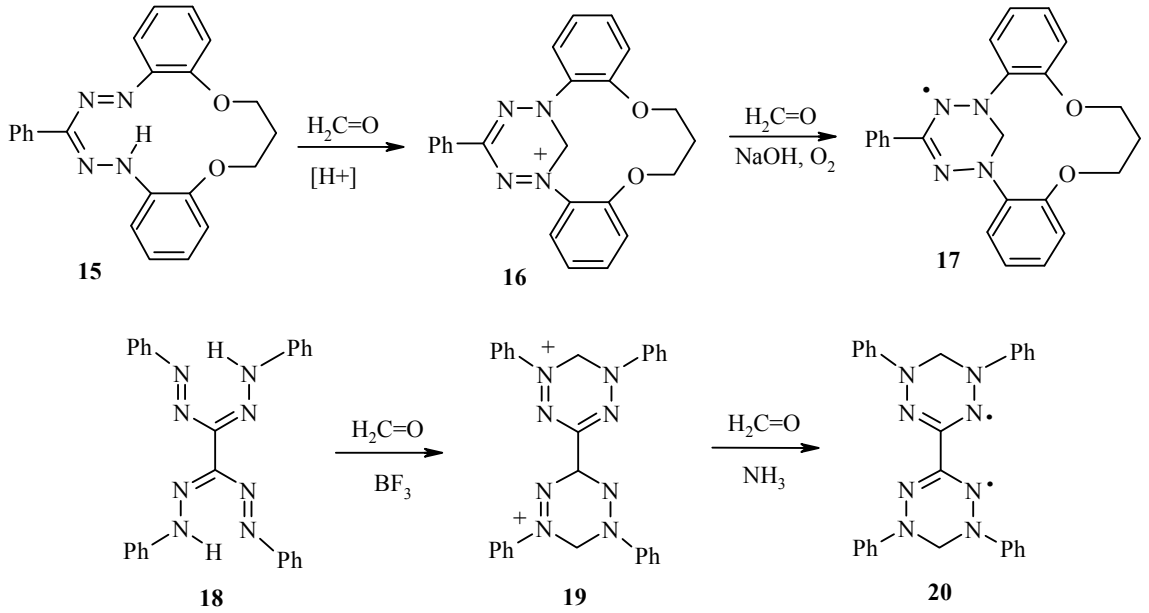
Many of the 5-alkylformazans **6** are unstable substances, and often their production is not even attempted since sometimes it even requires the creation of special conditions (an oxygen-free medium, etc.) [2-4, 7]. Even under the conditions of alkylation they can undergo cyclization to tetrahydrotetrazines **2**. The transformation of the isolated 5-alkylformazans **6** to leucoverdazyls **2** can be realized at elevated temperature by the action of acids or bases [4, 7]. The leucoverdazyls **2** can also be oxidized easily to the verdazyls **4** since the alkaline medium promotes both cyclization of the 5-alkylformazans **6** to the leucoverdazyls **2** and their oxidation to the verdazyls **4**.

The susceptibility of the 5-alkylformazans **6** to cyclization and the stability of the leucoverdazyls **2** are determined by the nature of the aryl substituents in the initial formazans **1** [2-4, 7, 16]. The presence of electron-withdrawing substituents in the R^1, R^5, and even R^3 groups hinders both alkylation of the formazans **1** and the subsequent processes. Thus, in contrast to the 1,3,5-triphenylformazan (**1a**) the alkylation of 1,5-di-phenyl-3-(pentafluorophenyl)formazan with MeI leads only to the leucoverdazyl **2a** (R* = Me, $R^1 = R^5 = Ph$, $R^3 = C_6F_5$). Under the same conditions the isomeric 5-(pentafluorophenyl)-1,3-diphenylformazan forms a mixture of N-methylfurazan **6b** and leucoverdazyl **2b** (R* = Me, $R^1 = R^3 = Ph$, $R^5 = C_6F_5$), while the alkylation of 1,5-di(pentafluorophenyl)-3-phenylformazan stops at the stage of 5-methylformazan **6** (R = H, $R^1 = R^5 = C_5F_5$, $R^3 = Ph$) [38]. Electron-withdrawing substituents R^3 at the *meso* position of the formazan increase the stability of the tetrahydrotetrazines **2**, while donating substituents promote their oxidation to the verdazyls **4**. Accepting substituents in the aryl rings at the nitrogen atoms hinder alkylation of the formazans **1** but increase the stability of the verdazyl radicals **4**, wich allows the use of such verdazyls for various purposes [2-4, 7]. In acidic media the transformation of 5-alkylformazans **6** as a rule results in the formation of verdazylium salts **5**, which can be easily reduced to the verdazyls **4** [7].

The second method for the synthesis of verdazyls from formazans is based on reactions with aldehydes, mainly formaldehyde, in an alkaline medium. As a rule the process takes place in one stage but in two steps with change of the pH of the medium from acidic at the beginning to alkaline in the second step [2-4, 7, 39-41]. This is the most convenient and economically favorable method for the production of verdazyls and makes it possible to synthesize them even with unsaturated substituents such as propargyloxyphenyl [39]. If the reaction of formazans **1** with formaldehyde is conducted in $CHCl_3$ good yields of the verdazyls **4** are obtained [40]. In an acidic medium or in the presence of BF_3 the verdazylium salts **5** are formed, and they are reduced to verdazyls (by alcohols in an alkaline medium, hydroxylamines, ascorbic acid, hydrazine etc.) [7, 38-40].

The formaldehyde method was used for the synthesis of the macrocyclic verdazyl cation **16** and, then, the verdazyl **17** [41] from the crown-formazan **15** and of 6,6'-diverdazyl **20** from the diformazan **18** through the stage of the dication **19** (Scheme 7).

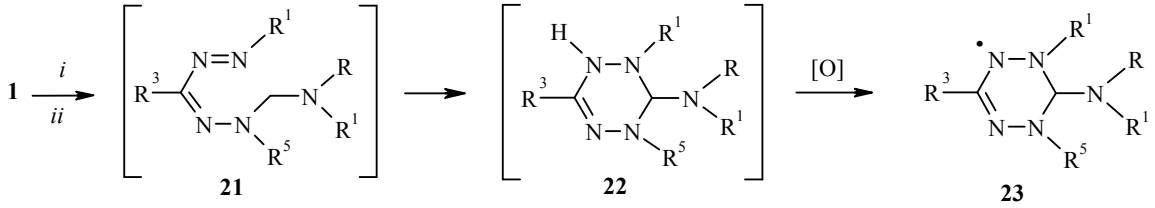
Scheme 7



15 16 17 18 19 20

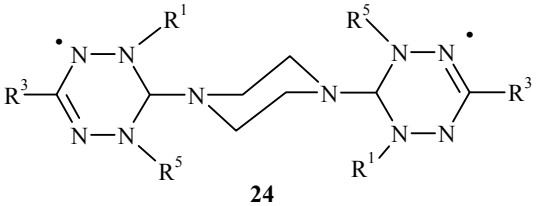
The synthesis of verdazyls from formazans by the Mannich reaction, developed by Kuhn and Trischmann, has also been developed significantly (Scheme 8) [3, 4, 7]. Here, in no case were the intermediate 5-(R,R^1-aminomethyl)formazans **21** and 3-(R,R^1-amino)leucoverdazyls **22** isolated. Many verdazyls **23** containing the most varied disubstituted amino groups at position 3 were obtained by this method using a mixture of the dialkylamines or azacycles (piperidine, morpholine, etc.) and formaldehyde. In place of the mixture of amine and formaldehyde it is also possible to use aminomethylal $Me_2NCH_2NMe_2$ [7]. In its place Katritzky and co-workers proposed to use 1-(dialkylaminomethyl)benzotriazoles (Btz^1NRR^1) (Scheme 8) [17]. This made it possible to greatly diversify the nature of the substituents in the targeted verdazyls **23** since symmetrical and unsymmetrical dialkylamino [methylbenzylamino, methyl(2-furyl)amino, etc.] as well as heterocyclic fragments (morpholino, piperidino, tetrahydroisoquinolino) were used. This is the method by which the diverdazyls **24**, where the dihydrotetrazine fragments are linked at positions 3 by a piperazine ring, were obtained (Scheme 8).

Scheme 8



21 22 23

i = H_2C=O + HNR_2: NR_2 = NMe_2, $NAlk_2$, $N(CH_2CH_2)_2X$, were X = bond, CH_2, O, NR;
ii = Btz^1–NRR^1: NRR^1 = NMe_2, NEt_2; N(Me)Bn, $N(Me)CH_2$Fur-2-yl, $N(CH_2CH_2)_2X$; X = CH_2, O

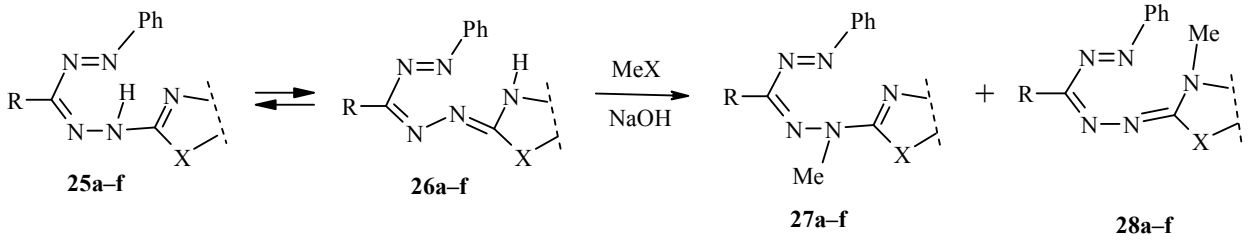


24

The functionalization of verdazyls as a method for the synthesis of new types is based on the use of more readily available formazans. One version is based on the ability of verdazyls to enter into chemical reactions without loss of the radical center, and another on their preliminary conversion to leucoverdazyls **2**.

Heterylformazans are used significantly less than the aryl analogs for the synthesis of the corresponding N-heterylverdazyls. Only the production of benzothiazol-2-yl-, pyrid-2-yl-, and (in greatest detail) tetrazol-5-ylverdazyls has been studied [3, 4, 7, 42, 43]. In many cases the alkylation of 1-aryl-5-heterylformazans **25a-f**, differing in the nature of the heterocycle, is complicated by preferential alkylation in the heterocycle, which can be explained by change of the basicity center or "formazan **25**–formazene **26**" tautomerism. As a result of this the heterocyclic formazans **28a-f**, incapable of closure of the dihydrotetrazine ring by 1,6-electrocyclization of the 1,2,4,5-tetraazahexa-1,3,5-triene fragment, are formed instead of the 5-alkylformazans **27a-f** or N-heterylverdazyls. The more stable the formazene tautomer **26**, the more likely is the formation of the alkylated formazenes **28**. Thus, formazans having a phthalazine ring at position 5 exist exclusively as 1-aryl-3-R-5-(4-R-1,2-dihydrophthalazin-1-ylidene)-formazans (formazenes **26d**,**e**) and not as 5-phthalazinylformazans **25d**,**e**, as suggested in the early papers. During alkylation they only form the phthalazinylidene isomers **28d**,**e** (Scheme 9) [4].

Scheme 9

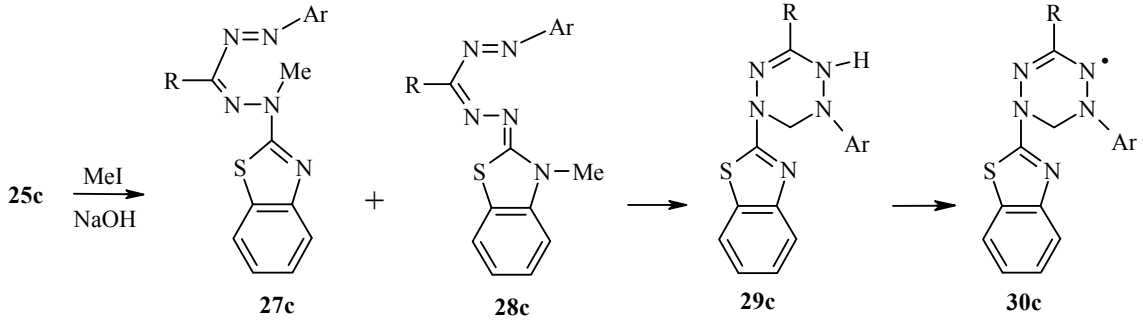


25a–f **26a–f** **27a–f** **28a–f**

R = Me, Ph; **a** 5-hetaryl = 1-alkylbenzimidazol-2-yl; **b** benzoxazol-2-yl; **c** benzothiazol-2-yl; **d** phthalazin-2-yl; **e** 4-chlorophthalazin-2-yl; **f** 1-methyltetrazol-5-yl.

The behavior of 1-aryl-5-(benzazol-2-yl)-3-methylformazans **25a-c** is ambiguous and depends on the nature of the heterocycle (1-alkylbenzimidoles, benzoxazoles, and benzothiazoles) and the alkylation conditions. Thus, the formazenes **28a-c** were obtained exclusively during the action of MeI in an alkaline medium. A more detailed study of the alkylation of 1-aryl-5-(benzothiazol-2-yl)-3-R-formazans **25c** (R = Me, Ph) showed that with 30% NaOH in ethanol a mixture of three difficultly separable products is obtained: The $(E)_{3,4}$- and $(Z)_{3,4}$-isomers of 5-methylformazans **27c** (R = Me, Ph) and 5-(3-methylbenzothiazol-2-ylidene)-formazenes **28c** (R = Me, Ph). Under the conditions of preparative chromatography the leucoverdazyls **29c** and verdazyls **30c** (R = Me, Ph, Ar = 4-$O_2NC_6H_4$), formed during elution from the methylated formazans **27c** (Scheme 10), were also obtained [43].

Scheme 10



27c **28c** **29c** **30c**

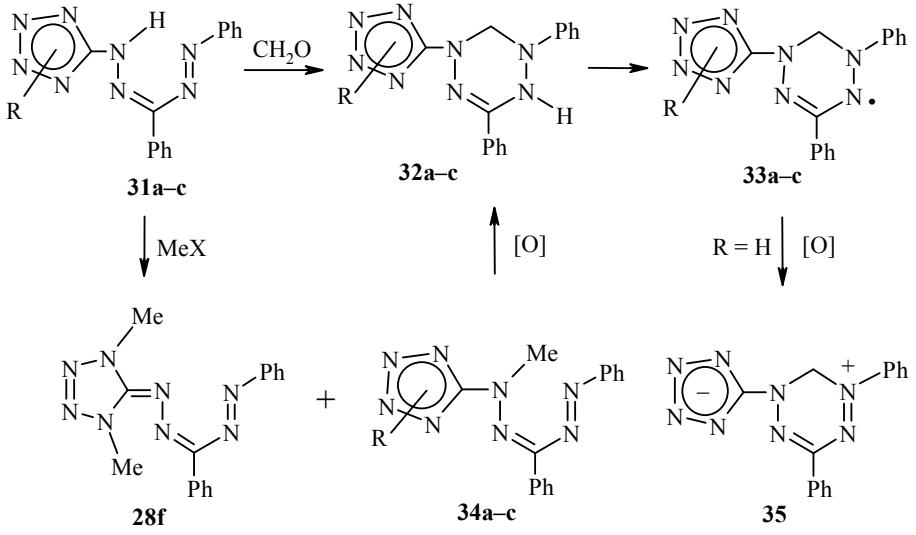
R = Me, Ph, Ar = Ph, 4-$O_2NC_6H_4$

The formazenes **28c** are thermally stable, whereas the 5-alkyl-5-heterylformazans **27c** are converted on heating into the leucoverdazyls **29c**. Here the formazans **27c** having a phenyl substituent (R = Ph) undergo cyclization more readily (even at room temperature) than the formazans **27c** with a 3-methyl fragment (R = Me), while (benzothiazol-2-yl)leucoverdazyls **29c** are more stable than the aryl analogs and are only converted into the verdazyls **30c** by the action of PbO_2 [4, 43].

When 5-(1-alkylbenzimidazol-2-yl)- and 5-(benzoxazol-2-yl)-1,3-diphenylformazans **25a** and **25b** were treated with diazomethane only the products from alkylation in the heterocycle **28a**,**b** were isolated. In this case too 5-(benzothiazol-2-yl)-3-methyl-1-phenylformazan **25c** forms 5-(benzothiazol-2-yl)-3,5-dimethyl-1-phenylformazan **27c** (R = Me, Ar = Ph), which is converted into the verdazyl **30c** (R = Me, Ar = Ph) under the synthesis conditions [4, 7, 43].

Of all the known heterylformazans 5-(R-tetrazol-5-yl)formazans **31a-c** have been studied in greatest detail; they are capable of being converted into (tetrazol-5-yl)leucoverdazyls **32a-c** and (tetrazol-5-yl)verdazyls **33a-c** containing unsubstituted and also 1-methyl- and 2-methyl-substituted tetrazolyl groups (Scheme 11). Leucoverdazyls **32a-c** were obtained both during alkylation of the formazans **31a-c** and during their reaction with formaldehyde [4, 7, 42].

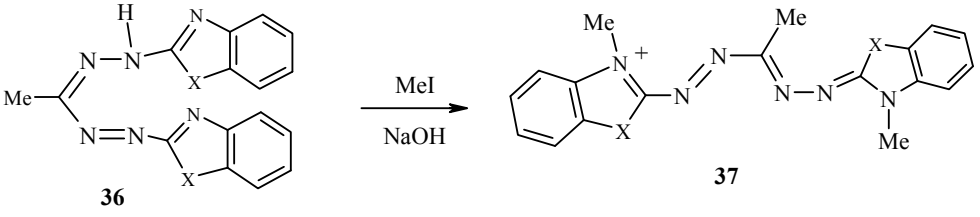
Scheme 11



31–34 a R = H, **b** R = 1-Me, **c** R = 2-Me

The 5-methyl-5-(1(2)-methyltetrazol-5-yl)-1,3-diphenylformazans **34b**,**c** are more stable than the 5-aryl analogs. Only on heating do they undergo cyclization to (methyltetrazolyl)leucoverdazyls **32b**,**c**, the spontaneous transformation of which to 2-(methyltetrazol-5-yl)verdazyls **33b**,**c** also does not occur (Scheme 11). For their production it is necessary to use an oxidizing agent, usually PbO_2.

Scheme 12



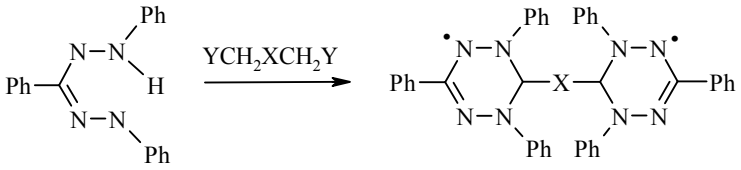
X = S, O, NR

2,4-Dihetaryl-1,2,3,4-tetrahydro-1,2,4,5-tetrazines of type **2** (R^1, R^5 = Het) and the corresponding verdazyls **4** (R^1, R^5 = Het) have evidently not yet been described. The first attempts at their synthesis by alkylation of 1,5-diheteryl-3-R-formazans **36** resulted in the production of tetraazapentamethinecyanines **37**, i.e., alkylation occurred at the nitrogen atoms of both heterocycles [4, 7, 42].

Formazans proved to be excellent precursors for the synthesis of the most structurally varied types of verdazyls, which differed not only in the nature of the substituents in the tetrahydro-1,2,4,5-tetrazine ring but also in the number of verdazyl fragments in the molecule. Such free radical structures were required for study of the molecular paramagnetic susceptibility and exchange interactions in polyradicals. A large number of both monoverdazyls and di-, tri-, tetra-, and polyverdazyls with various linking units both at the carbon atoms and at the nitrogen atoms of the tetrahydro-1,2,4,5-tetrazine ring were therefore synthesized [2-4, 7, 9, 15, 17, 19]. By using initial formazans with various structures and various methods of synthesis a large range of diverdazyls containing various spacers between the positions of the 3,3'-, 4,4'-, or 6,6'-hexahydrotetrazine ring (Scheme 13), including the above-mentioned compounds **7**, **20**, and **24** and also derivatives of [2,2]paracyclophanes, were obtained. 1,3,5-Tris-(verdazyl-6-yl)benzene was synthesized by methylation of the trisphenylhydrazone of 1,3,5-triformylbenzene, and later tetrakis(verdazyl-6-yl)methane was synthesized from tetrakis(4-formylphenyl)methane by the formaldehyde method.

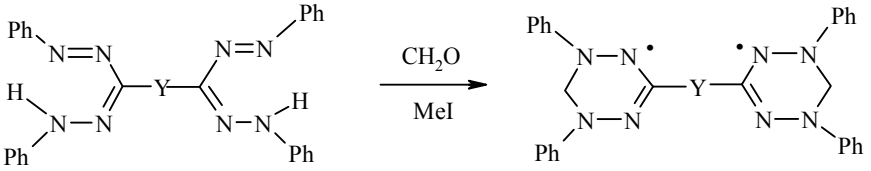
Scheme 13

3,3'-Diverdazyls:



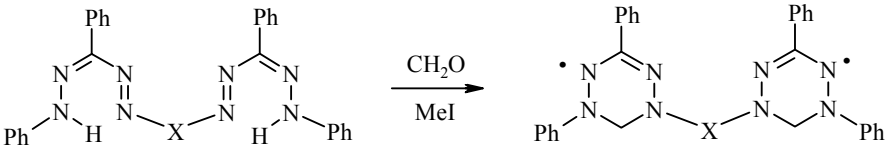
X = 1,3-C_6H_4; $(1,4\text{-}C_6H_4)_m$, m = 1, 2, 3, 4; 1,5- and 2,6-naphthylene;
2,2'- and 3,3'-diphenyldiyls and [2,2]paracyclophanediyls; $(CH_2CH_2)_4$; $(CH_2)_n$, n = 2, 4

6,6'-Diverdazyls:



Y = bond (e.g., **20**); $(CH_2)_4$; $C_6H_4O(CH_2CH_2OCH_2CH_2)_mOC_6H_4$, m = 1, 2, 3

4,4'-Diverdazyls:

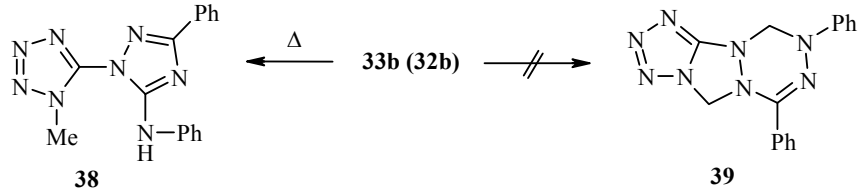


X = 1,4-$(C_6H_4)_2$; 1,3-C_6H_4; 1,4-C_6H_4

1-Substituted 1,2,3,4-tetrahydro-1,2,4,5-tetrazines **3**, which are of interest as biologically active compounds, are rarely obtained from formazans in one stage. It is more convenient to synthesize them by the reaction of verdazyls **4** with haloalkanes (even haloalkanes such as adamantyl bromide) or with adamantyl tosylates and 1,3-dicarbonyl compounds; this increases the synthetic potential of formazans as precursors in the synthesis of heterocycles. 1-R-Tetrahydrotetrazines **3** are formed with high yields from verdazyls and with many free radicals and also with organolithium, organoaluminum, and organomagnesium compounds, although in these cases the nature of the solvent plays a very important role. Here some solvents having multiple bonds can take part in the reaction as a third component [7, 44].

The synthesis of 1,2,3,4-tetrahydro-1,2,4,5-tetrazine derivatives of types **2**-**5** from formazans can be complicated by side processes. They can be converted into other products depending on nature of the initial formazan or on the reaction conditions (heat, etc.). Thus, triarylverdazyls can disproportionate at elevated temperatures into leucoverdazyls **2** and 3-anilino-1,5-diaryl-1,2,4-triazoles. At higher temperature the latter eliminate aniline and are converted into 1,5-diaryl-1,2,4-triazoles [1, 4, 7]. A similar process was observed not only during heating but also during storage and even during the production of 4-(1-methyltetrazol-5-yl)-2,6-diphenylverdazyl **33b** of its leuko base **32b**. Both substances are easily transformed into 5-anilino-1-(1-methyltetrazol-5-yl)-1,2,4-triazole **38** (Scheme 14), which was earlier erroneously taken as 6,8-diphenyltetrazolo[1,5-*a*][1,2,4]triazolo[1,2-*c*][1,2,4,5]tetrazine **39**. Erroneous data on the synthesis of the tricycle **39** were repeated more recently in the reviews [8, 45].

Scheme 14

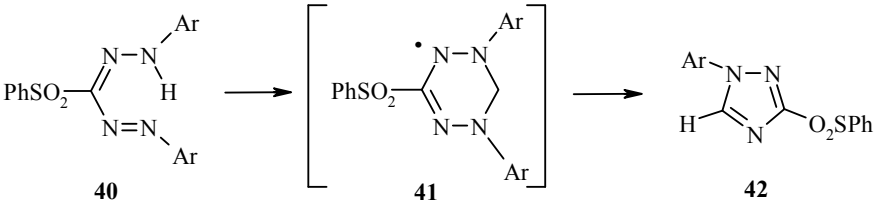


38 **39**

Similar transformations sometimes hinder the synthesis of the targeted products from the corresponding formazans. Thus, during methylation of the formazan **31b** with dimethyl sulfate the yield of the leucoverdazyl **33b** amounted to only 31%, while in the formaldehyde method it was only 17%. 1,5-Diphenyl-1,2,4-triazole was isolated as the main product.

During the treatment of 1,5-diaryl-3-(phenylsulfonyl)formazans **40** with formaldehyde and sodium sulfite the 1-aryl-3-phenylsulfonyl-1,2,4-triazoles **42** were obtained exclusively instead of the expected verdazyls **41** [1, 46]:

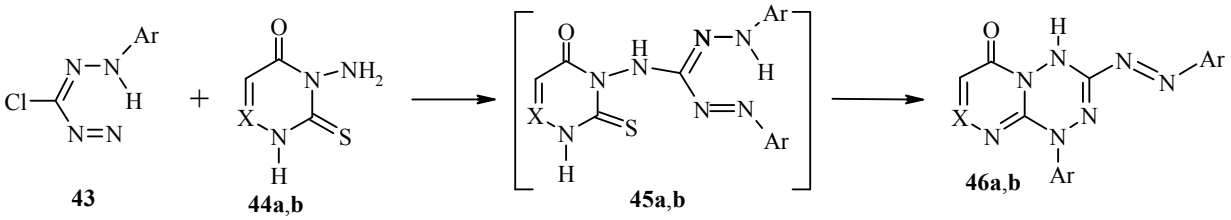
Scheme 15



40 **41** **42**

1,5-Diaryl-3-haloformazans **43** were excellent precursors in the synthesis of annelated derivatives of 1,2,3,4-tetrahydro-1,2,4,5-tetrazines, according to path *d* in Scheme 1. For example, with thioxopyrimidines and thioxo-1,2,4-triazinones **44a**,**b** they react initially at the amino group, and the intermediately formed 3-(heteryl-amino)formazans **45a**,**b** undergo intramolecular cyclization to the pyrimido[1,2-*b*]- and 1,2,4-triazino[4,3-*b*]-1,2,4,5-tetrazines **46a**,**b** [47]:

Scheme 16

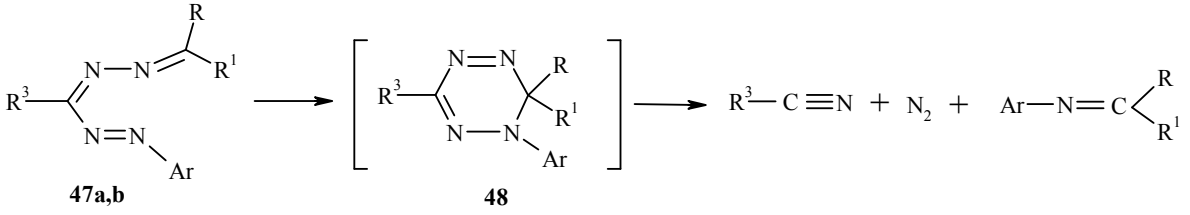


X = CH, N

1.2. 1,6-Dihydro- and 1,4-Dihydro-1,2,4,5-tetrazines

Examples of the use of certain types of formazans, such as 1-aryl-5-(R,R'-methylene)formazans (formazenes **28a-c** and **47a**,**b**), in the synthesis of 1,6-dihydro-1,2,4,5-tetrazine derivatives **48** by path *b* of Scheme 1 have not yet been described. The reason for this may be the instability of the heterocyclic system. Thus, the ease of transformation of the keto- **47a** (R and $R^1 \neq H$) and aldoformazenes **47b** ($R^1 = H$) to nitriles and arylamines was explained by just this factor (Scheme 17) [4]. It was assumed that the intermediate product of the 1,6-electrocyclization of the 1,2,4,5-tetraazahexa-1,3,5-triene system of formazenes **47a**,**b** has the structure of 1,6-di-hydro-1,2,4,5-tetrazine **48**, which soon undergoes retro-[2+2+2] cyclization.

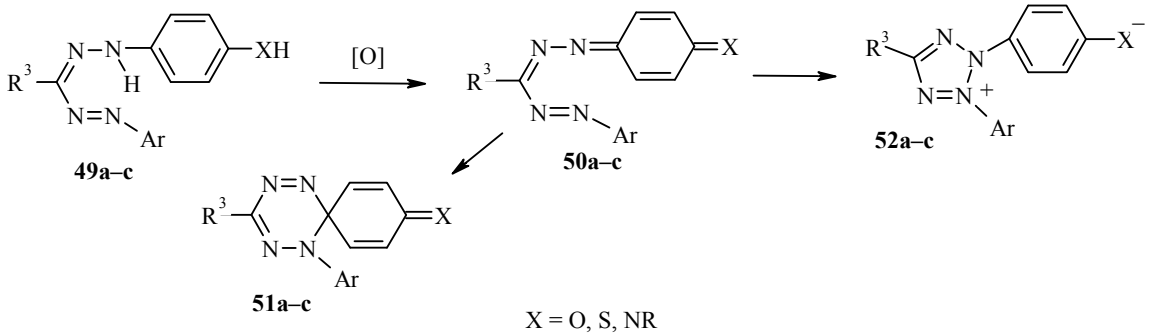
Scheme 17



a R = Ar, Alk; R^1 = Ar; **b** R = Ar, Alk; R^1 = H

More recently it was shown that 1-aryl-5-(hetarylidene)formazans (e.g., of the **26**, **28**, and **37** types) are more stable than the ketoformazenes **47a** with two free substituents, while the aldoformazenes **47b** undergo preferential 1,5-electrocyclization [1, 4]. In view of these facts it can be assumed that by changing the nature of the ylidene fragment in the formazenes **47a**,**b** or in the heteroformazenes **28** it is possible to obtain stable derivatives of 1,6-dihydro-1,2,4,5-tetrazine **48**. For example, during the oxidation of the formazans **49a-c** containing functional groups XH (X = O, S, NR) in 5-aryl substituent it will be possible to obtain the formazenes **50a-c**, which may be converted into the stable spiro derivatives 1,6-dihydro-1,2,4,5-tetrazines **51a-c** (Scheme 18). Finally, it is not impossible that the polyazapolyene system of the formazenes **50a-c** will prove more susceptible to transformation to the tetrazolium salts **52a-c**.

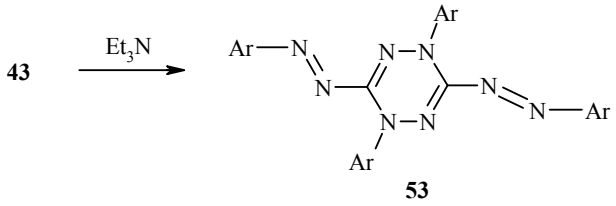
Scheme 18



X = O, S, NR

Derivatives of 1,4-dihydro-1,2,4,5-tetrazine have only been obtained from formazans by Shawali and co-workers [48]. Using 1,5-diaryl-3-chloro-1,2,4,5-tetrazines **43** as precursors, they obtained 1,4-diaryl-3,6-bis-(arylazo)-1,4-dihydro-1,2,4,5-tetrazines **53** (Scheme 19). On the basis of kinetic data the authors postulated a two-step mechanism for this reaction according to path *i* of Scheme 1, making it possible to classify it as a special case of path *d* or path *e* (Scheme 1). The authors' conclusion is not inconsistent with known data to the effect that the transformation of hydrazonoyl halides, to which the 3-chloroformazans **43** belong, into 1,4-dihydro-1,2,4,5-tetrazines can take place in various ways [4]. Apart from the familiar [3+3] dimerization of nitrile imines, which can be generated from the corresponding precursors, linear 1,3-addition of the initial halogenohydrazone (in this case 3-chloroformazan **43**) to the obtained nitrile imine quite often occurs and is followed by intramolecular cyclization of the intermediate product with hydrazidine structure [4].

Scheme 19

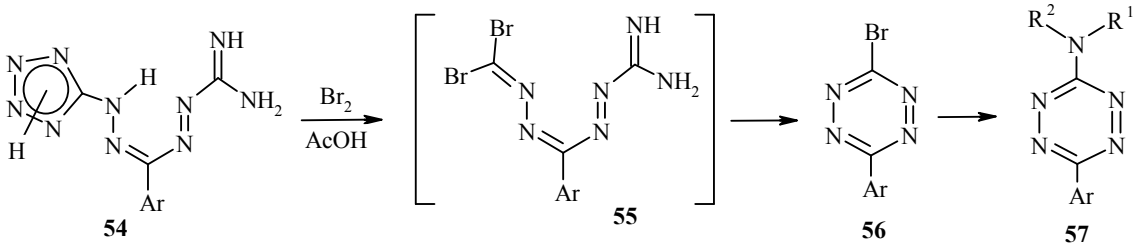


53

1.3. 1,2,4,5-Tetrazines

The synthesis of 3,6-disubstituted 1,2,4,5-tetrazines by path *c* of Scheme 1 has only been realized from 1(5)-amidino-5(1)-(1-H-tetrazolyl)formazans **54** on account of the specific characteristics of the tetrazole ring and amidine fragment attached to the nitrogen atom. As far back as the nineteenth century it was known that (1H-tetrazol-5-yl)hydrazine and its hydrazones open the tetrazole ring under the action of bromine with the formation of derivatives with dibromomethyleneimino groups, while the amidine fragment is readily detached from the nitrogen atom of all types of hydrazones, including from position 5 of formazans [1, 4, 6, 8]. The presence of both fragments in one molecule led to the result that the formazans **54** form 6-aryl-3-bromo-1,2,4,5-tetrazines **56** when treated with bromine in AcOH through, evidently, the formazenes **55** (Scheme 20). This method was the first method by means of which it was possible to synthesize unsymmetrically disubstituted 1,2,4,5-tetrazines **56** and, from them, other derivatives such as the amines **57** having high antimalaria activity.

Scheme 20

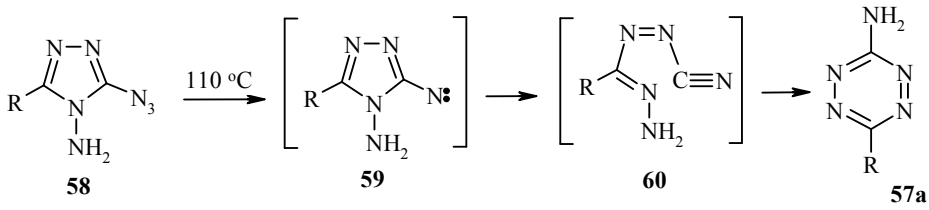


54 **55** **56** **57**

Amino derivatives of 1,2,4,5-tetrazine, but only those not substituted at the amino group [e. g., the aminotetrazine **57a** ($R^1 = R^2 = H$)], are also produced during the thermolysis of 4-amino-3-azido-5-R-1,2,4-triazole **58**. Its production in this case is explained by the formation of the intermediate nitrene **59** at the first stage and, then, 1-cyano-3-R-formazan **60**, in which the usual addition of the amino group to the nitrile group is realized (Scheme 21) [8].

On account of the low stability of formazans with an unsubstituted N-5 atom [4] and the specificity of the substituent at the N-1 atom the reaction is probably only of theoretical significance.

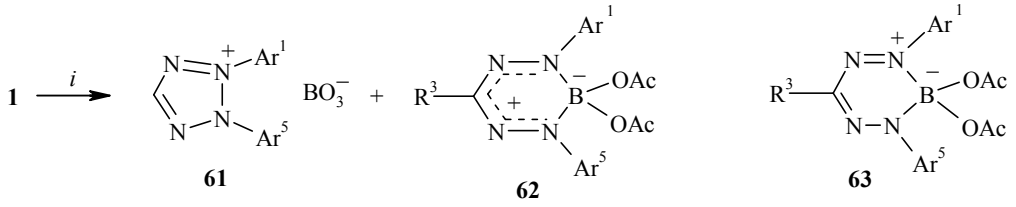
Scheme 21



2. 1-BORA-2,3,5,6-TETRAZINES

1,5-Diaryl-3-R-formazans **1** (R^1, R^5 = Ar) are the only precursors in the synthesis of boratetrazines (Scheme 22) [4, 13, 49-51]. Earlier it was observed that triaryltetrazolium tetrafluoroborates are formed exclusively in the reaction of 1,3,5-triarylformazans with $BF_3 \cdot OEt_2$ [1, 4]. With diboran tetraacetate Stepanov and co-workers were able to obtain 2,4,6-triaryl-1,1-diacetoxyboratetrazines of types **62** or **63** [50, 51]. Oxidative processes were also observed here, and the yield of the triaryltetrazolium borate **61** (80%) significantly exceeded the yield of boratetrazine **62** (20%). It was subsequently possible to increase the yield of the boratetrazines **62** and to bring 1,5-diaryl-3-R-formazans unsubstituted at position 3 or having Cl, Me, or NO_2 [51], 2-furyl, or 5-nitro-2-furyl- groups [49] at this position into this reaction.

Scheme 22



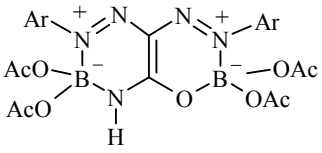
i = $B(OH)_3$ + AcOH + Ac_2O; R^3 = Ph, 4-Tol, H, Me, Cl, NO_2, Fur-2-yl, 5-NO_2-2-Fur-2-yl;
$R^1 = Ar^1$ and $R^5 = Ar^5 = RC_6H_4$; R = H, 4-Me, 4-NO_2, 4-OMe, 4-Br, 4-SO_2NH_2

Under the conditions of this reaction the nitrile group of 1,5-diaryl-3-cyanoformazans is hydrolyzed to an amide group. Here, together with the boratetrazine **62** (R^3 = C(=O)NHAc) the bicyclic product **64** was also isolated in a ratio of 3:1. Each of its rings was formed with the participation of different fragments of the formazan and different heteroatoms of the amide group; this makes it possible to achieve the coupling of two different heterocycles [50].

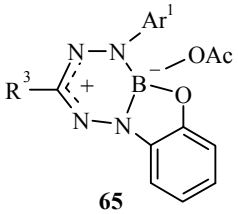
If there is an OH group at the *ortho* position of the aryl ring of 1,5-diaryl-3-R-formazans it takes part in coordination of the boron atom with the formation of the complex **65** (Scheme 23). However, if there are OH groups at other positions of the benzene rings they are only acylated during the reaction.

The structural analogy between the 1-bora-2,3,5,6-tetrazine complexes **62** and the verdazyl cations **5** gives rise to the similarity in their properties. For example, with cobaltocene they are rapidly reduced to the green "boraverdazyl" radical anion **66** [51]. The low stability of the obtained radical anions **66** has reduced the interest in this redox system.

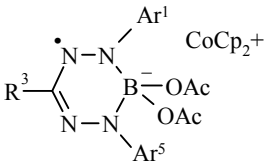
Scheme 23



64



65



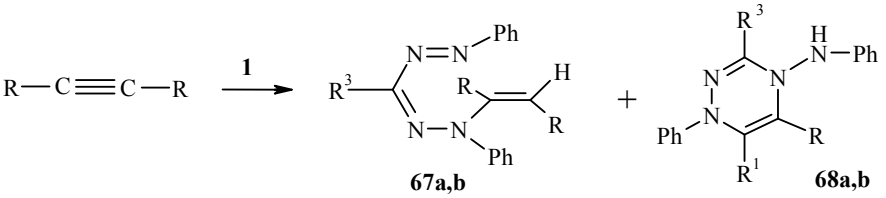
66

3. 1,2,4-TRIAZINES AND BENZO-1,2,4-TRIAZINES

3.1. 1,2,4-Triazines

Derivatives of 1,2,4-triazine can be obtained from formazans in several ways (paths *g* and *h* in Scheme 1) [2-4, 10-12]. Thus, two competing reactions occur in the reaction of 1,5-diaryl-3-R-formazans **1** ($R^1 = R^5$ = Ph, R = Ph, Me) with acetylenes: Addition of the NH group of the formazans at the triple bond with the formation of 1,5-diaryl-5-vinylformazans **67a**,**b** and Diels–Alder reaction with the 1,2,4-triazabuta-1,3-diene system of formazan, leading to 4-arylamino-1,4-dihydro-1,2,4-triazines **68a**,**b** (Scheme 24). The factors determining the preference for one or other of the directions have hardly been established at all, and the synthetic potential of these reactions has not yet been evaluated. The role of the substituents in the aryl rings is not clear, but it can be supposed that donor substituents will promote the formation of the triazine ring. In 3-methylformazans the probability of cycloaddition is higher than in 3-H-formazans [12].

Scheme 24



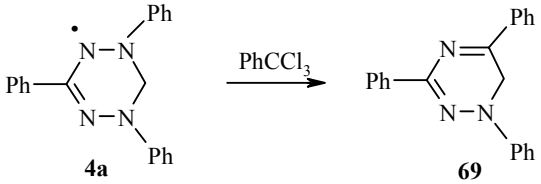
67a,b **68a,b**

R = COOMe; **a** R^3 = Ph, **b** R^3 = Me

Derivatives of the 1,4- and 1,6-dihydro-1,2,4-triazine types **68** and **69** (Scheme 25) are poorly accessible but are in great demand on account of their high biological activity [10, 11]. The synthesis of 1,4-dihydro-1,2,4-triazines of type **68** according to Scheme 24 is the first method for their production and is extremely promising on account of the availability of both precursors.

The direct synthesis of 1,6-dihydro-1,2,4-triazines of type **69** from formazans has not been described, but they are easily obtained through the verdazyls **4**. Thus, when heated with benzotrichloride 2,3,6-triphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazinyl (verdazyl **4a**), readily obtainable from 1,3,5-triphenylformazan **1a**, forms 1,3,5-triphenyl-5,6-dihydro-1,2,4-triazine **69** (Scheme 25) [7]. The reaction presumably takes place through

Scheme 25

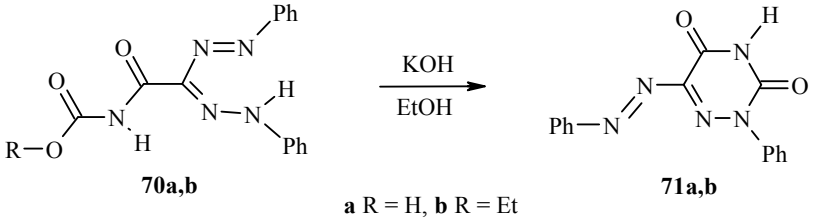


4a **69**

phenyl carbene. In spite of the small yield (20%) of the 1,2,4-triazine **69** this method for the synthesis of 1,6-dihydro-1,2,4-triazine derivatives may prove extremely fruitful if more rational methods are used for generation of the carbenes.

In an alkaline medium the 1,5-diphenylformazans **70a**,**b**, which have a carbamoyl group at position 3, undergo cyclization with high yield to 1-phenyl-3-(phenylazo)-1,2,4-triazine-4,6-diones **71** (Scheme 26) [2-4].

Scheme 26



70a,b **71a,b**

a R = H, **b** R = Et

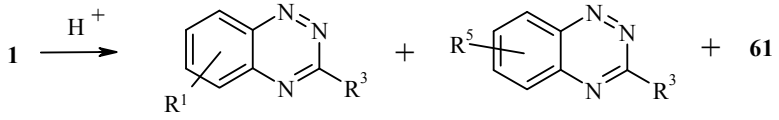
According to [4, 11] the best method for the synthesis of 1,2,4-triazines is the condensation of amidrazones with 1,2-dicarbonyl compounds, but examples of the participation of 3-amino-1,5-diarylformazans, which are representatives of a very interesting group of amidrazones, in this reaction were not found in the literature.

3.2. Benzo-1,2,4-triazines

The synthesis of benzo-1,2,4-triazines **72a** by intramolecular cyclization of 1,5-diarylformazans (by path *h* in Scheme 1) under the influence of acids is the most widely used method for their production (Scheme 27) (see [2-5, 10, 11] and references therein). Many derivatives of benzo-1,2,4-triazine have found use in medicinal chemistry–particularly the fluorine-containing compounds with high antiviral activity [5, 10, 11, 52, 53] – and this has prompted study of the reaction in recent years.

Usually, H_2SO_4 in AcOH is used for the cyclization of 1,5-diarylformazans **1**, but other versions, such as BF_3 in AcOH, etc., have been described [2-5, 10, 11]. This method is often called the "formazyl method" or the "Bamberg synthesis of benzo-1,2,4-triazines **72**," although Pechman was also among the original pioneers of the reaction.

Scheme 27



72a **72b**

R^3 = Alk, Ar, Ac, Bz, COOEt, Ar–N=N–, Het, Cl, NH_2

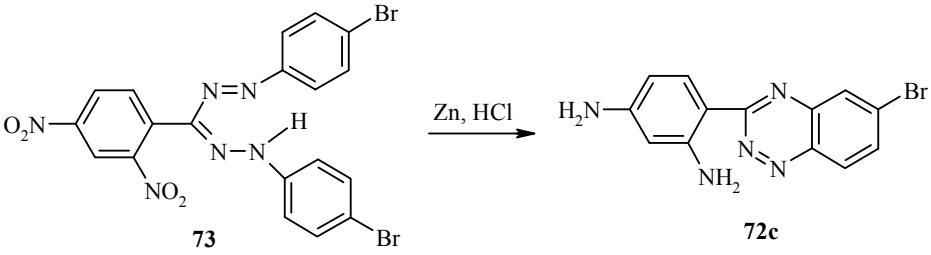
Symmetrical 1,5-diarylformazans **1** ($R^1 = R^5$), including those containing strong accepting groups in the aryl rings, naturally form one isomer of benzo-1,2,4-triazine **72**, although sometimes oxidative processes intervene, and tetrazolium salts **61** and, rarely, phenazines are isolated as side products. With substituents R^1 and R^5 similar in electronic nature (e.g., R^1 = Ph, R^5 = 4-C_6H_4Me, 4-C_6H_4OMe) two benzo-1,2,4-triazines **72a** and **72b** are formed; their ratio is determined by the relative contents of the 5-NH and 1-NH tautomers of the

initial formazan in the reaction mixture [4, 5]. As known [4, 54, 55], if there is a significant difference in the electron-accepting character of the substituents at N-5 and N-1 the formazans **1** are not susceptible to 5-NH–1-NH tautomerism and exist in the form of only one tautomer. In such cases only one benzo-1,2,4-triazine **72a** is formed in the reaction [2-5, 10, 11], e.g., in the cases of R^1 = Ph and R^5 = 4-$HO_3SC_6H_4$, R^1 = Ph and R^5 = 3,2-$F_2C_6H_3$, or R^1 = Ph and R^5 = 3-F-4-(AlkO)C_6H_3 [52, 53]. 5-Naphthyl-1-phenylformazans undergo cyclization in the naphthalene ring to naphtho-1,2,4-triazines.

Substituents at position 3 can also substantially affect the ratio of the isomeric benzotriazines **72a**,**b**. Thus, during the action of H_2SO_4 on 3-H- and 3-methyl-5(1)-(4-methoxyphenyl)-1(5)-phenylformazans both isomeric benzotriazines **72a** (R^3 = H, Me; R^1 = H) and **72b** (R^3 = H, Me; R^5 = 6-OMe) were isolated, while the 3-phenyl analog under the same conditions only formed the 6-methoxy-2-phenyl isomer **72b** (R^3 = Ph, R^5 = 6-OMe).

The nature of the substituent at the *meso* position of the formazan group can affect the direction of cyclization but usually has little effect on the yield of the benzotriazines **72**. The 3-alkyl-, 3-acyl-, and 3-hetaryl-substituted 1,5-diaryl-formazans undergo cyclization to benzo-1,2,4-triazines just as readily as the 1,3,5-triarylformazans [2-5, 10, 11]. The 3-(arylazo)-, 3-(5-nitro-2-furyl)-, and 3-(1-phenylquinolinium-4-yl)-substituted 1,5-diarylformazans are also no exception. In these cases, however, the presence of several accepting groups in the 3-aryl substituent can increase the stability of the formazans to the action of acids as a result of a sharp decrease in their basicity. Thus, 1,5-bis(4-bromophenyl)-3-(2,4-dinitrophenyl)formazan **73** does not change even in hot hydrochloric acid, whereas the transformation of both nitro groups into amine groups is accompanied by rapid cyclization to 6-bromo-2-(2,4-diaminophenyl)benzo-1,2,4-triazine **72c** with a good yield.

Scheme 28



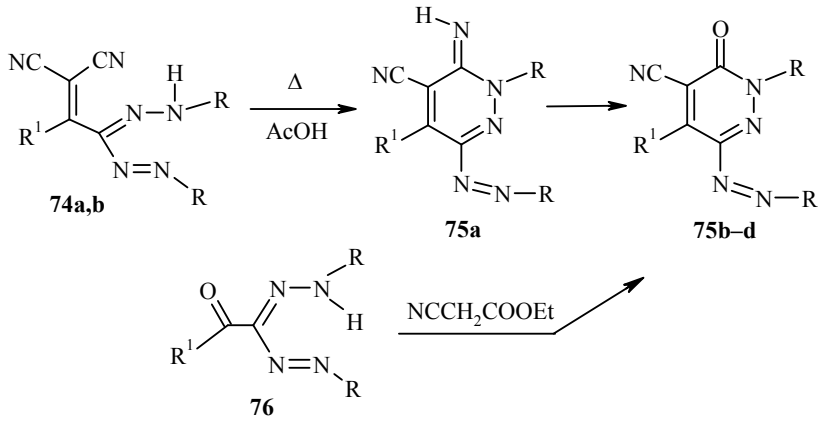
73 **72c**

The presence of the arylhydrazone or oxime fragments in the *meso* position of formazans of type **1** (R^3 = RC=NOH, RC=NNHAr) changes the direction of the reaction, and 1,2,3-triazole derivatives **32** are formed with high yields by the action of acids instead of benzo-1,2,4-triazines [1-4].

4. PYRIDAZINES AND ANNELATED PYRIDAZINES

The use of formazans as a special type of hydrazone in the synthesis of pyridazines is based on the classical reaction of intramolecular addition at multiple bonds in the γ-position to the hydrazone group (path *d* in Scheme 1) [4]. Thus, 1,5-diaryl- and 1,5-di(3-phenylpyrazol-5-yl)-3-(2,2-dicyano-1-phenylethenyl)-formazans **74a**,**b** (Scheme 29), like the initial 3-phenylpyrazol-5-yl derivatives and arylhydrazones of 3,3-di-cyano-2-phenylacrolein [4], are converted into the dihydropyridazines **75a** with high yields when heated in AcOH. In the case of pyrazolyl-substituted formazans **74a** the reaction stops at the stage of the imines **75a**, while the aryl analogs **74b** are hydrolyzed to 2,3-dihydropyridazin-3-ones **75b**.

Scheme 29



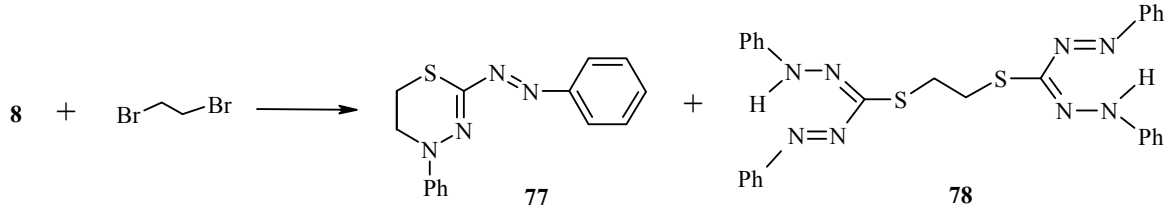
74a, **75a**: R = 3-phenylpyrazol-5-yl, R^1 = Ph; **74b**, **75b–d** R = Ar, **75 b** R^1 = Ph, **c** R^1= H, **d** R^1= Et; **76** R = Ar, R^1 = Et

It is difficult to stop the condensation of 3-acyl-1,5-diarylformazans **76** with cyanoacetic esters at the stage of (1,5-diarylformazan-3-yl)cyanoacrylic esters (analogs of 3-vinylformazans **74**). Immediate intramolecular acylation to 2,3-dihydropyridazin-3-ones **75d** in the reaction mass occurs [56].

5. 1,3,4-THIADIAZINES AND BENZO-1,3,4-THIADIAZINES

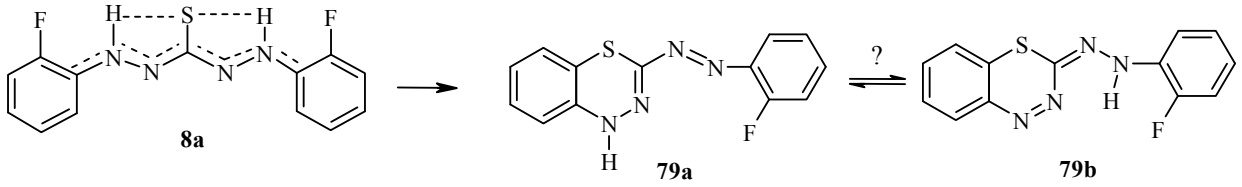
As already mentioned above [1], if there are characteristic groups in the substituents R^1, R^3, and R^5 of the formazans **1** various intramolecular cyclizations are possible: between the substituent in R^3 or in $NR^{1(5)}$ and the NH fragment of the formazan, between the substituent in $NR^{1(5)}$ and the fragment in R^3, etc., including the formation of six-membered and larger rings (Scheme 1, paths *d-f*) [3, 4, 14]. Thus, the alkylation of the dithizone **8** with 1,*n*-dihaloalkanes (*n* = 2-4) leads to thiadiazacycles through 3-(bromoalkylulfanyl)formazans. In particular, in its reaction with 1,2-dibromoethane 4-phenyl-2-(phenylazo)-5,6-dihydro-1,3,4-thiadiazine **77** and a small amount of the bissulfide **78**, the product of the bisalkylation of two molecules of the dithizone **8** at the sulfur atoms, are formed.

Scheme 30



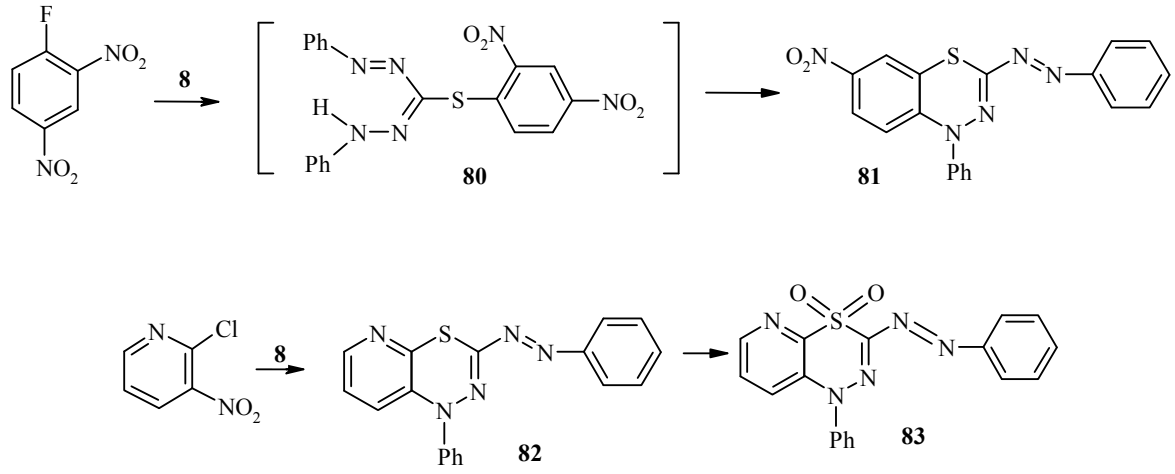
When boiled in alcohols 2,2'-difluorodithizone **8a** undergoes cyclization to 2-(2-fluorophenylazo)-1,3,4-benzothiadiazine **79**, the properties of which, particularly the **79a**–**79b** tautomerism, have not yet been fully studied [14].

Scheme 31



An analogous product is formed even more readily during treatment of the dithizone **8** with 2,4-dinitrofluorobenzene. Even at room temperature the product from arylation at the sulfur atom (the formazan **80**) undergoes cyclization to 1,3,4-benzothiadiazine **81** (Scheme 32). The ease with which the unactivated nitro group is substituted in these cases is surprising. Similar cyclization occurs with somewhat greater difficulty if 2-chloro-3-nitropyridine is used in this reaction and leads to the formation of pyrido[3,2-*e*]-1,3,4-thiadiazine **82** (Scheme 32) [14]. It must be emphasized that 2-(arylazo)benzo-1,3,4-thiadiazines **79**, **81**, and **82** are themselves multipurpose precursors in the synthesis of S,S-dioxide (e.g., the thiadiazine **83**) and amino derivatives of benzo-1,3,4-thiadiazines [4, 14].

Scheme 32



The formation of 3-(arylazo)-1,2,4-thiadiazines from the products of the oxidation of dithizone (from dehydrodithizone and its analogs) discussed in details in the first part of this review [1] and can provide a further illustration of the synthetic potential of the production of various heterocyclic systems using various types of formazans.

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