CYCLIZATION OF AZINES WITH BIFUNCTIONAL NUCLEOPHILES – A ONE-STEP ROUTE TO CONDENSED HETEROCYCLES (REVIEW)

V. N. Charushin, M. G. Ponizovskii, and O. N. Chupakhin

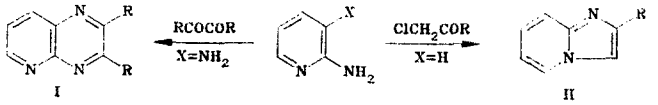
UDC 547.821'852.9(047)

Nucleophilic diaddition and disubstitution in the azine series with the participation of bifunctional reagents, the result of which is the formation of condensed heterocycles, were examined.

Heterocyclic compounds of the azine series constitute a significant class of organic substances that have a number of useful properties, the most important of which is their biological activity [1].

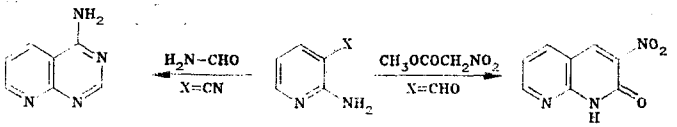
The methods for the synthesis of heterocycles with a condensed azine ring are based chiefly on cyclization reactions, the overall diversity of which can be reduced to several types.

The reactions of azines that contain two nucleophilic groupings (one of which may be a ring nitrogen atom) with bifunctional electrophilic compounds make up the first group. The condensations of α-amino azines leading to azoloazines I, which were examined in detail in a previous review [2], the condensations of o-diaminoazines with dicarbonyl compounds leading to condensed pyrazines II [3], and other reactions that have already become traditional methods for the synthesis of heterocyclic compounds may serve as examples of such cyclization reactions.



I II

A second large group of cyclization reactions in which azines that have one nucleophilic grouping and one electrophilic grouping and suitably constructed cyclizing agents participate also remains outside the scope of our review. Cyclization of this type are most characteristic for o-amino carbonyl derivatives of azines [4-6] and their o-amino nitriles [7].



The present review is devoted to an examination of the principles and peculiarities of cyclization reactions of a third type, viz., the reactions of azines and azinium cations with bifunctional nucleophilic reagents, the reaction centers of which exist in the XH form (X = C, N, O, S). Both cyclizations based on the replacement of two o-oriented groups that leave readily and reactions involving the diaddition of bifunctional nucleophiles to the azine ring that also lead to condensed azines will be included in the sphere of our examination.

The review encompasses the literature data from the last 5-10 yrs on the most widely used reactions of azines with 1,3- and 1,4-bifunctional nucleophiles, as a result of which annelation of five- and six-membered rings occurs.

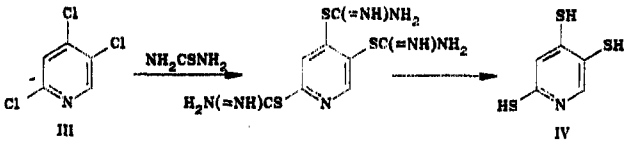
REACTIONS OF AZINES WITH DINUCLEOPHILES THAT DO NOT LEAD TO CYCLIC COMPOUNDS

The reactions of azines with dinucleophiles do not always lead to cyclic compounds; they may be complicated by the formation of noncyclic products, and this reaction pathway sometimes

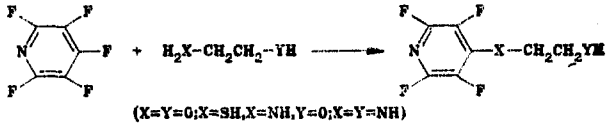
S. M. Kirov Ural Polytechnic Institute, Sverdlovsk 620002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1011-1026, August, 1985. Original article submitted February 20, 1984.

0009-3122/85/2108-0839$09.50

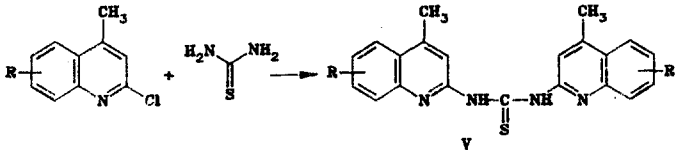
becomes the chief process. Thus halo-substituted pyridines III react with thioureas to give the corresponding trimercapto derivatives IV; even in the case of replacement of two o-oriented chlorine atoms, the formation of cyclic compounds was not observed [8, 9].



Only one fluorine atom undergoes substitution in the reaction of pentafluoropyridine with diverse dinucleophiles [10]. The second reaction center of the bifunctional nucleophile remains inert in this case



Cases in which both reaction centers of the dinucleophile participate in the reaction, but in which two molecules of the heterocycle are linked together to give diazinyl derivatives V, are also known [11-13].



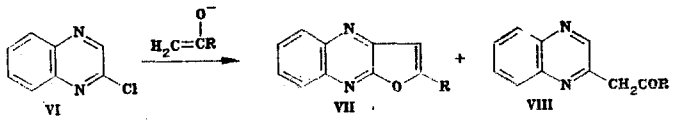
The examples examined above show that, despite the ability of dinucleophiles to react at both centers, the presence of a suitably reactive and suitably constructed azine is still necessary for realization of the cyclization reactions.

CYCLIZATION REACTIONS OF AZINES WITH DINUCLEOPHILES THAT PROCEED WITH REPLACEMENT OF GROUPS THAT LEAVE READILY OR WITH THE PARTICIPATION OF SIDE SUBSTITUENTS

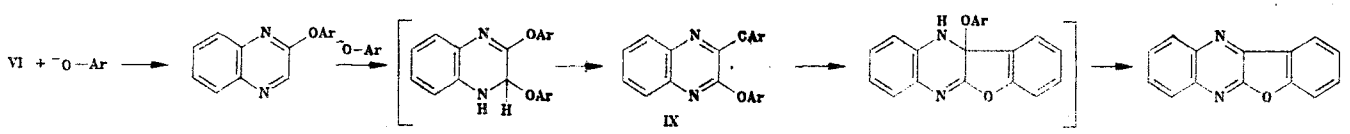
Annelation of Five-Membered Rings

The introduction of a second nitrogen atom in the heteroring significantly increases the ability of azines to react with nucleophiles. In a number of cases one observes a qualitative shift, which is manifested in a tendency for some azines to undergo diaddition and disubstitution reactions. This is most characteristic for pyrazine and quinoxaline derivatives [3, p. 169]. The increased reactivity of 1,4-diazines creates the prerequisites for the formation of cyclic compounds in reactions with dinucleophiles, which proceed particularly readily if groups that leave readily, such as a halogen atom, are present in the 2 and 3 positions.

Furoazines. In contrast to 2-chloroquinoline [14-16], 2-chloroquinoxaline (VI) reacts with enolates of ketones to give furo[2,3-b]quinoxalines VII as the principal products [17, 18]. 2-Quinoxalinyl ketones VIII are wide products.

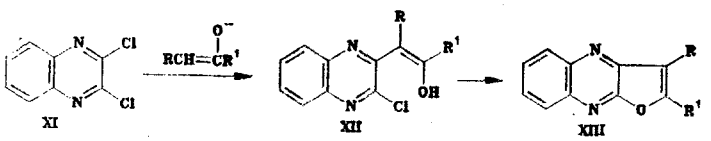


The reaction of 2-chloroquinoxaline with phenoxide anions, which, in the opinion of Anderson and Cheeseman [19], includes the formation of intermediate IX with subsequent intramolecular substitution, proceeds similarly.



IX

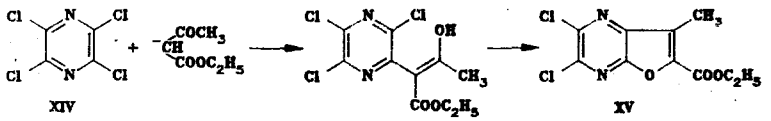
2,3-Dichloro-1,4-diazines XI react with C,O-ambident nucleophiles to give cyclic compounds under milder conditions and in higher yields than in the case of monohalo-substituted 1,4-diazines [20].



XI XII XIII

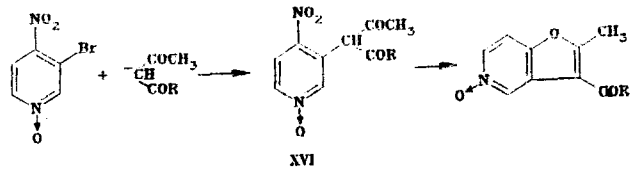
Iijima and Hayashi [20] have shown that furo[2,3-b]-quinoxalines XIII are obtained only when quinoxalinyl ketones XII, which are formed in the first step as a result of replacement of chlorine by the carbanion, are capable of enolization. Otherwise, exclusively the product of C substitution of one chlorine atom of XII is formed.

It is not surprising that the cyclization reactions of 1,4-diazines with β-dicarbonyl compounds that readily generate anions and have higher percentages of the enol forms proceed even more readily. Thus tetrachloropyrazine (XIV) reacts smoothly with acetoacetic ester to give furo[2,3-b]pyrazine XV [21].

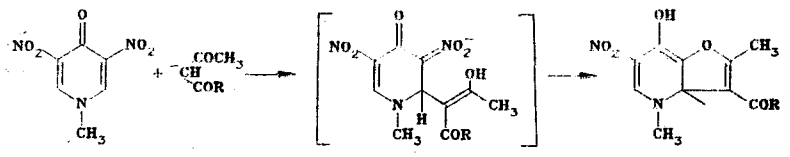


XIV XV

Annelation of the furan ring was also observed in the reactions of β-dicarbonyl compounds with monoazines when they were activated by strong acceptor groupings such as a nitro group. The ability of nitro azines to undergo cyclization with β-dicarbonyl compounds was demonstrated in [22-24].



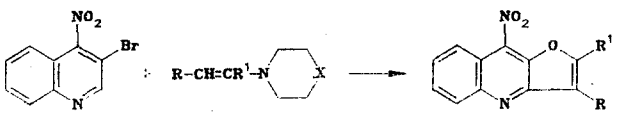
XVI



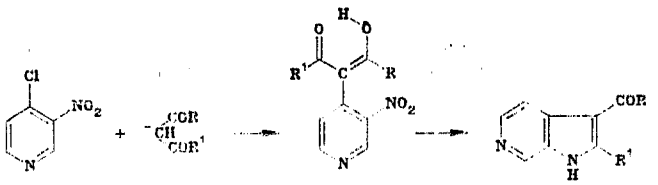
XVII

It is assumed [22-24] that either Michael adduct XVII or a product (XVI) of substitution of halogen is formed in the first step, after which intramolecular cyclization with replacement of the nitro group occurs.

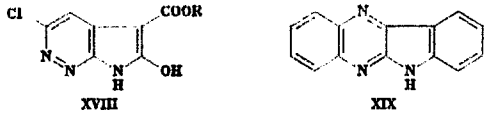
The furan ring is also annelated in the reaction with enamines due to hydrolysis of the iminium intermediate to an enol [23]. Let us point out that nucleophilic substitution of hydrogen rather than the nitro group, as one might have expected, occurs in this case.



Pyrroloazines. A number of studies [25-27] dealing with the cyclization reactions of β-dicarbonyl compounds with 4-chloro-3-nitropyridine have been made by L. N. Yakhontov and co-workers. These reactions differ from those described above with respect to the second step, in which a nitrogen atom, rather than an oxygen atom, enters into the resulting ring, which leads to azaindoles.



The same authors have described [28] the synthesis of diazaindoles XVIII from 3,4,6-trichloropyridazine and malonic esters.

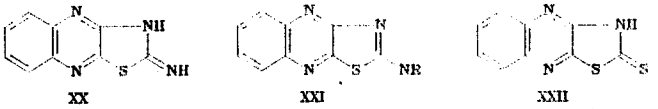


XVIII XIX

Indoloquinoxalines XIX were obtained along with noncyclic compounds in the reaction of 2-chloroquinoxaline with arylamines [29]. It is assumed that the mechanism of their formation is similar to that examined above for benzofuro[2,3-b]quinoxalines X [19].

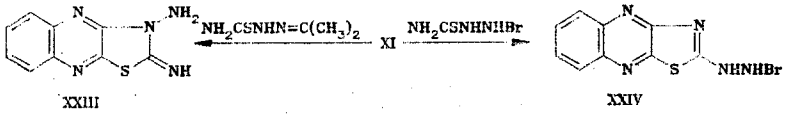
2,3-Dichloroquinoxaline (XI) is one of the most suitable subjects for ring annelation by virtue of the high lability of both chlorine atoms and their equivalence. It is therefore not surprising that a significant number of studies dealing with the cyclization reactions of azines with dinucleophiles have recently been made precisely on the basis of this diazine.

Thiazolazines. Methods for the synthesis of various thiazolo[4,5-b]quinoxalines XX-XXII based on cyclization reactions of dichloroquinoxaline (XI) with thioureas [30-33] and dithiocarbamates [32, 33] have been developed.



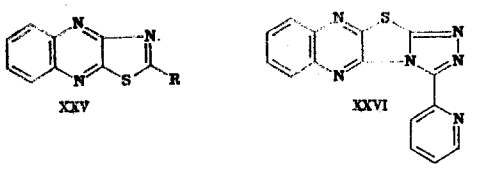
XX XXI XXII

The pathway of the cyclization of dichloroquinoxaline (XI) with thiosemicarbazides depends on the substituent. Thus acetone thiosemicarbazone forms 3-amino-2-imino-2,3-dihydrothiazolo [4,5-b]-quinoxaline (XXIII) [31], whereas bromothiosemicarbazide gives 2-hydrazino derivative XXIV [34].



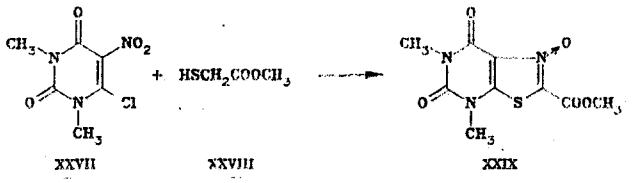
XXIII XI XXIV

Thiazolo[4,5-b]quinoxalines XXV and XXVI are also formed in the cyclization of 2,3-dichloroquinoxaline with thiocarboxylic acid amides [32, 35], as well as with 1H-2-mercaptotriazoles [32, 34, 36, 37].



XXV XXVI

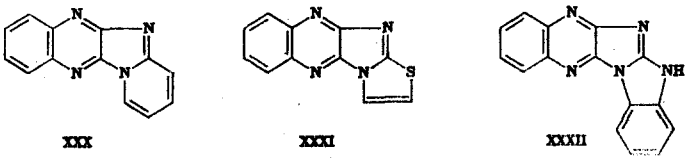
The problem of the annelation of the thiazole ring was solved in an interesting way in [37]. Senda and co-workers used the reaction of chloronitropyrimidine XXVII with mercaptoacetic acid ester XXVIII, which is essentially one of the few examples of the participation of a bifunctional nucleophile in cyclization reactions.



XXVII XXVIII XXIX

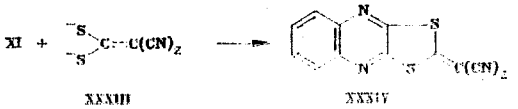
In the course of the reaction, the mercapto group replaces chlorine, and the adjacent CH-active group forms a ring with the side substituent.

Azines Annelated by Other Five-Membered Heterocycles. A number of examples of annelation of the imidazole ring to the quinozaline ring in reactions with cyclic amidines, to which α-amino derivatives of nitrogen heterocycles are related, and with the same 2,3-dichloroquinoxaline have been described [35].



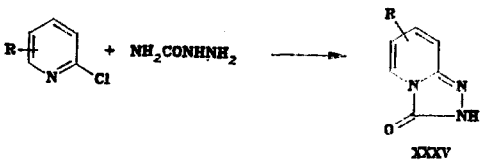
XXX XXXI XXXII

Salts (XXXIII) of geminal dimercaptans are used for the annelation of the 1,3-dithiolane ring of XXXIV [38].



XXXIII XXXIV

Thus variation of the 1,3-bifunctional nucleophiles makes it possible to obtain various systems with a condensed five-membered ring on the basis of 2,3-dichloroquinoxaline and other chloro- and nitro-substituted azines. The pathway of such cyclizations can be predicted on the basis of the available literature data. However, unusual pathways in the cyclization of azines with dinucleophiles are also known. Thus the cyclization of 2-chloropyridine with semicarbazide, as a result of which 1,2,4-triazolo[4,3-a]pyridine XXXV is formed, was described in [39].

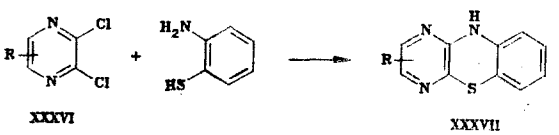


XXXV

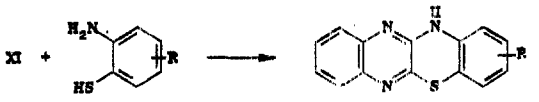
Annelation of Six-Membered Rings

Primarily two methods are used for the annelation of six-membered heterocycles to the azine ring: reactions of 1,4-bifunctional nucleophiles with -halo-substituted azines and with o-halonitroazines.

Phenothiazines. A significant amount of research has been based on the reactions of 2,3-dichloro-1,4-diazines; this is due to their high reactivities and the ease with which the structures of the resulting compounds can be determined as a consequence of the symmetrical character of the azine. The development of research on the cyclization of these azines with 1,4-N,S-dinucleophiles, which make it possible to obtain aza and benzo analogs of phenothiazine [40-45], has also been stimulated by the fact that highly active psychotropic substances have been found in this series [46].

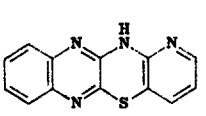


XXXVI XXXVII

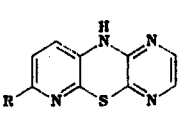


XXXVIII

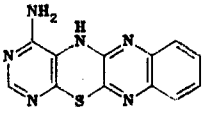
Heterocyclic o-amino thiols also react smoothly with dichloroquinoxaline XI to give, as a result of cyclization, triazaphenothiazines XXXIX and XL and tetraazaphenothiazines XLI and XLII, as well as triazolothiadiazinoquinoxalines XLIII [47-52].



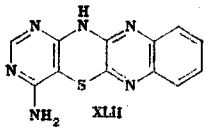
XXXIX



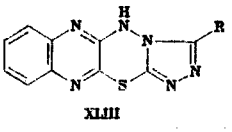
XL



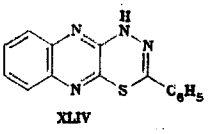
XLI



XLII



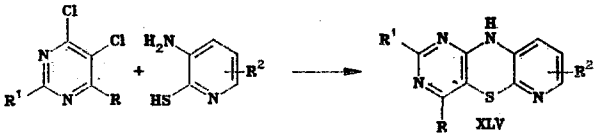
XLIII



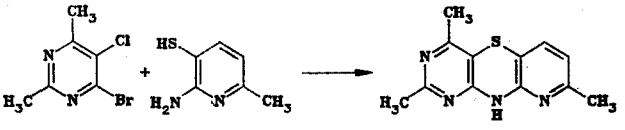
XLIV

Thiobenzoic acid hydrazide also displays the properties of a 1,4-N,S-dinucleophile, inasmuch as it gives thiadiazino-quinoxaline XLIV as a result of cyclization with 2,3-dichloroquinoxaline [53].

Triazaphenothiazines XLV and XLVI were obtained in the reaction of dihalopyrimidines with mercaptopyridines; in [54] it was shown that the first act in the cyclization, viz., replacement of the more labile halogen atom attached to the 4(6)-C atom by the amino group of the mercaptopyridine, does not depend on whether the competing N and S centers are located in the α or β positions relative to the nitrogen atom

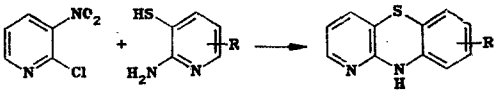


XLV

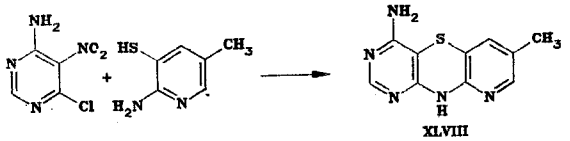


XLVI

The cyclizations of 2-chloro-3-nitropyridines and 4-chloro-5-nitropyrimidines with 1,4-N,S-dinucleophiles also lead to azaphenothiazines XLVII [56-60] and XLVIII [55].

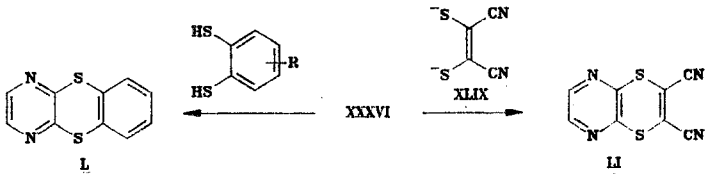


XLVII



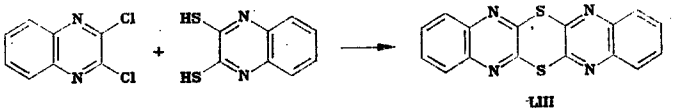
XLVIII

Dithiinoazines. Dithiinodiazines L and LI, which have high bactericidal and fungicidal activity, were obtained in the reaction of 2,3-dichloropyrazine with o-dimercaptobenzenes [44] and with salts (XLIX) of cis-1,2-dimercapto-1,2-dicyanoethylene [61].

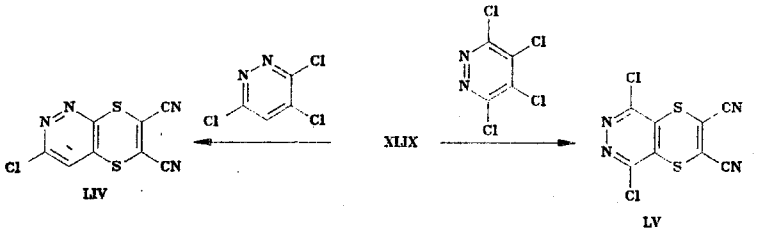


Double annelation of six-membered heterocycles to give LII is possible in the reaction of tetrachloropyrazine with 1,4 dinucleophiles [61, 62].

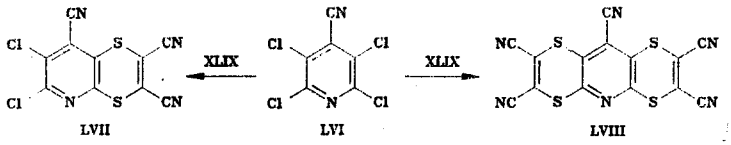
Five-ring system LIII, which contains a dithiin ring, was obtained by cyclization of 2,3-dichloro- and 2,3-dimercapto-quinoxalines [63].



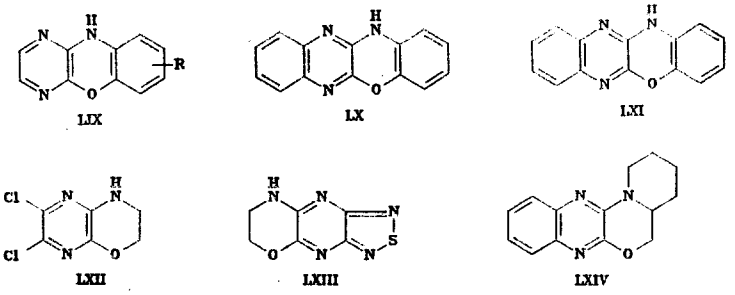
Polyhalo-substituted pyridazines react similarly with 1,4-S,S-dinucleophiles to give dithiinopyridazines LIV and LV [64].



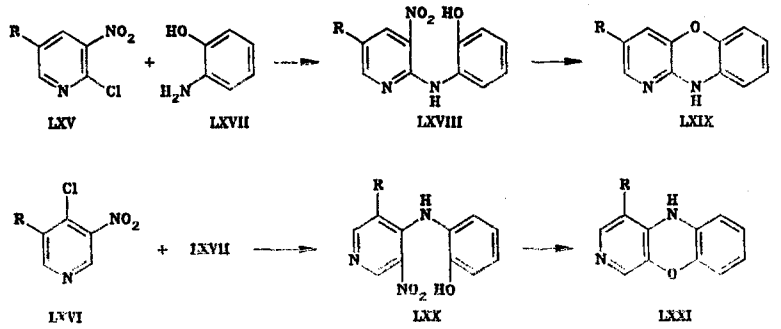
Only one polyhalo-substituted monoazine, viz., 4-cyano-2,3,5,6-tetrachloropyridine (LVI), which is capable of undergoing cyclization with dinucleophiles, is known; annelation of both one (LVII) and two (LVIII) dithiin rings with the pyridine ring is possible in the reaction with dimercaptodicyanoethylene (XLIX). Both LVII and LVIII display extremely high antibacterial activity [65, 66].



Oxazinoazines. Various 1,2-amino hydroxy compounds of the aliphatic, aromatic, and heteroaromatic series have been used for the construction of a 1,4-oxazine ring in reactions with 2,3-dichloro-1,4-diazines [44, 67-71]. Depending on the reagents used in the reaction, the following heterocycles LIX-LXIV were obtained:

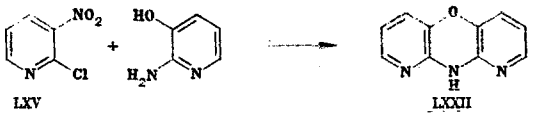


The cyclizations of 1,4-bifunctional nucleophiles with o-halonitroazines proceed in the same way as the reactions described above. The reactions of 2-chloro-3-nitro- (LXV) and 4-chloro-3-nitropyridine (LXVI) with o-aminophenol (LXVII), which lead to oxazine derivatives LXIX and LXXI, respectively, have been studied in detail [72, 73].



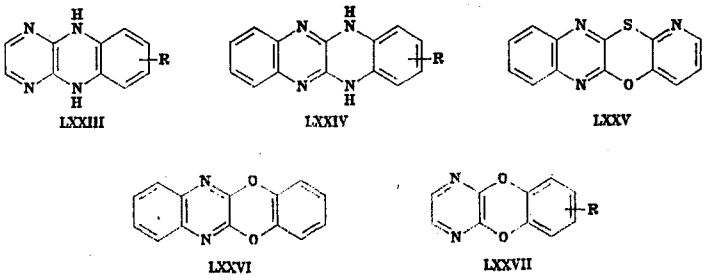
In a number of cases [72, 73] it was possible to isolate intermediates LXVIII and LXX, which were subsequently converted to three-ring compounds LXIX and LXXI. Some reactions of this sort were examined in a previous review [74], which was devoted to the synthesis of heterocyclic systems on the basis of intramolecular substitution of the nitro group.

The cyclization of chloronitropyridine LXV with 2-amino-3-hydroxypyridine proceeds via a similar scheme [75-77].

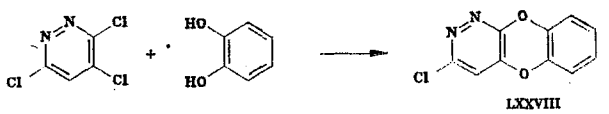


It is noted that the reactions of N,S- and N,O-dinucleophiles with azines proceed in two steps; the first step is always N addition and is followed by cyclization of the intermediate to give the corresponding heterocycle [67-69, 78, 79].

Azines Condensed with Other Six-Membered Heterocycles. There are not many studies [43, 78-80] devoted to the cyclization of 1,4-diazines with 1,4-N,N-, and -O,S-, and -O,O-dinucleophiles, which lead to pyrazine derivatives LXXIII and LXXIV [43, 78], oxathiin LXXV [79] and dioxin LXXVI, and LXXVII [43, 80], respectively.

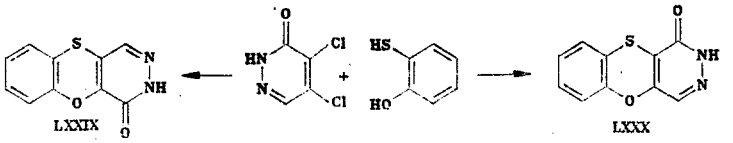


Even less attention has been directed to the cyclizations of o-dichloro-substituted 1,2- and 1,3-diazines with bifunctional nucleophiles. Except for the possibility of the formation of regioisomeric cyclization products in the case of unsymmetrical dinucleophiles, no fundamental differences in these cyclizations are observed. Thus the reactions of polyhalopyridazines lead to the corresponding dioxino- (LXXVIII) [80] and oxathiinopyridazines LXXIX and LXXX [81, 82].



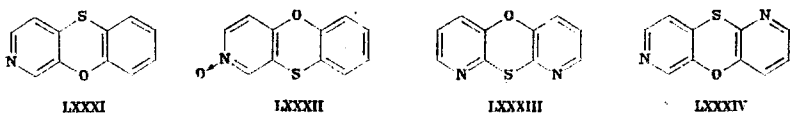
It was established that cyclizations with the participation of S,O-dinucleophiles also proceed in two steps through initial replacement of a halogen atom by a mercapto group and

subsequent replacement of the second halogen atom by phenoxide ion [81].



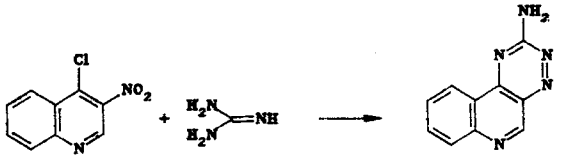
LXXIX LXXX

The cyclizations of nitrochloropyridines LXV and LXVI or their N-oxides with aromatic and heteroaromatic 1,4-S,O-dinucleophiles lead to oxathiin derivatives LXXXI-LXXXIV [83-86].



LXXXI LXXXII LXXXIII LXXXIV

A number of studies in which the nitrogen atom of the nitro group is included in the resulting ring have been made by Berenyi and co-workers [87-91]. Thus triazinoquinoline system LXXXVI is formed as a result of cyclization of 4-chloro-3-nitro-quinoline (LXXXV) with guanidine [87-89].

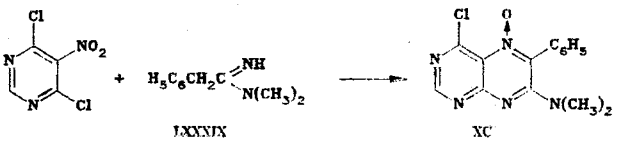


LXXXV LXXXVI

The participation of a group that leaves readily, such as a methoxy group, in cyclizations of azines with dinucleophiles was described by the same authors [90, 91].

LXXXVII LXXXVIII

The specific synthesis of pteridine N-oxide XC from 4,6-dichloro-5-nitropyrimidine and amidine LXXXIX, which was accomplished by Strauss and co-workers [92], clearly illustrates the possibilities of the application of such cyclizations.



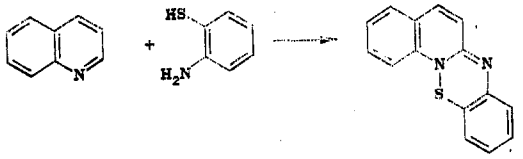
LXXXIX XC

CYCLIZATIONS OF AZINES WITH DINUCLEOPHILES BASED ON DIADDITION REACTIONS

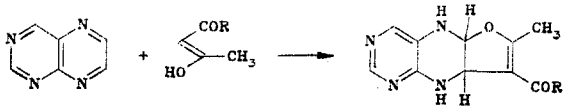
Methods that make it possible to carry out ortho cyclization with dinucleophiles without introducing any substituents into the azine have been developed in recent years. Annelation of diverse carbo- and heterocycles occurs as a result of these reactions of azines, just as in the reactions of o-chloro-, o-nitro-, and o-alkoxy-substituted compounds. Cycloadducts in the meta and para positions of the azine ring are also known, but they are, as a rule, unstable and undergo different sorts of transformations. The peculiarities of the formation of meta- and para-bonded cycloadducts in the reactions of azines with 1,3-ambident nucleophiles were examined in a previous review [93].

The overwhelming majority of ortho cyclizations take place in the 1,4-diazine series. As we have already noted, the ability of these compounds and particularly their quaternary salts to undergo diaddition of nucleophiles in the $C_{(2)}$ and $C_{(3)}$ positions [94, 95] creates

the prerequisites for the annelation of various five- and six-membered rings. Only one ortho cyclization at the azomethine bond of quinoline, the mechanism of which is not completely clear, is known for monoazines [96].

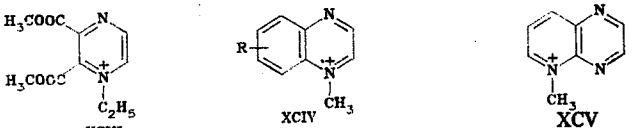


The reaction of pteridine (XCI) with β-dicarbonyl compounds [97], which leads to annelation of the furan ring to give XCII, was one of the first examples of the cyclization of 1,4-diazines with bifunctional nucleophiles.



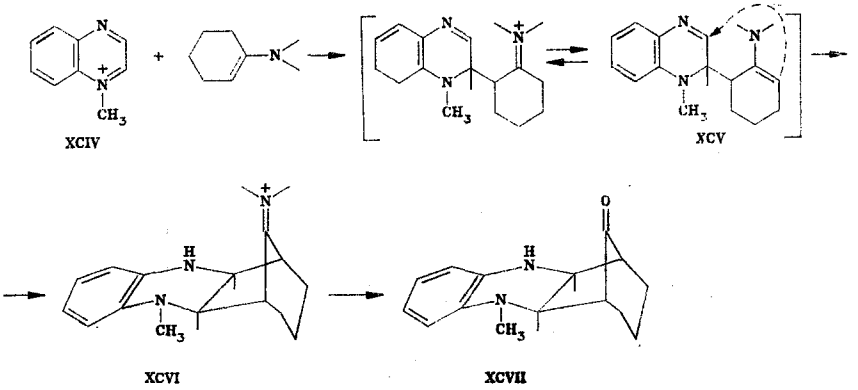
XCI XCII

Pyrazinium (XCIII) [98], quinoxalinium and benzo[f]- and benzo[g]quinoxalinium (XCIV) [93], and pyrido[2,3-b]pyrazinium (XCV) [99] cations were involved in the cyclization reactions of quaternary N-alkyl-1,4-diazinium salts with bifunctional nucleophilic reagents.



XCIII XCIV R=Alk, Hal, benzo XCV

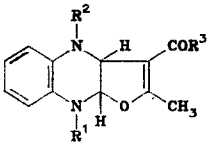
Most of the research was conducted with readily accessible quinoxalinium salts, to cyclization with which various 1,3- and 1,4-dinucleophiles with C,C-, C,N-, C,O-, N,N-, and N,S-nucleophilic centers were subjected. Thus enamines of cyclic ketones, which display the properties of 1,3-dicarbanionic reagents, react with the N-methylquinoxalinium cation (XCIV) to give cycloadducts XCVI and XCVII [100-102]. It is assumed that the cyclization proceeds in a stepwise manner through C adduct XCV, which, however, could not be detected [100-102].



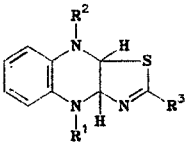
XCIV XCV XCVI XCVII

Just as condensed quinoxalines are formed in the reactions of 2,3-dichloroquinoxaline with 1,3-dinucleophiles, XCVIII, XCIX, and C were obtained in the cyclization of cation XCIV with β-diketones [103, 104], thioamides [105], and dithiocarbamates [106].

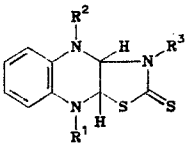
It should be noted that the reactions of N-alkyl-1,4-diazinium cations with bifunctional nucleophiles constitute a good supplement to methods for the synthesis of condensed systems on the basis of 2-chloro- and 2,3-dichloroquinoxaline, inasmuch as their hydrogenated derivatives, which are of independent interest from the point of view of the search for biologically active compounds, are formed as a result of such reactions.



XCVIII

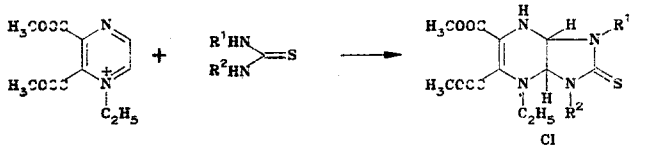


XCIX



C

However, there are also substantial differences between these groups of reactions. Thus in reactions with N-alkylpyrazinium and quinoxalinium cations thioureas display the properties of exclusively N,N'-dinucleophiles, forming imidazo[4,5-b]pyrazines CI and imidazo[4,5-b]quinoxalines CII as a result of cyclization [98], whereas in reactions with 2,3-dichloroquinoxaline [31-33] these compounds demonstrate the properties of N,S-bifunctional reagents.

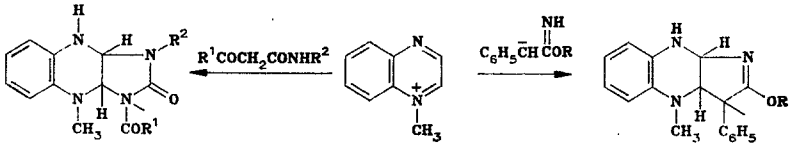


CI

CII CIII

Imidazo[4,5-b]quinoxalines CIII were also obtained in the reactions of the N-methylquinoxalinium ion with amidines [107].

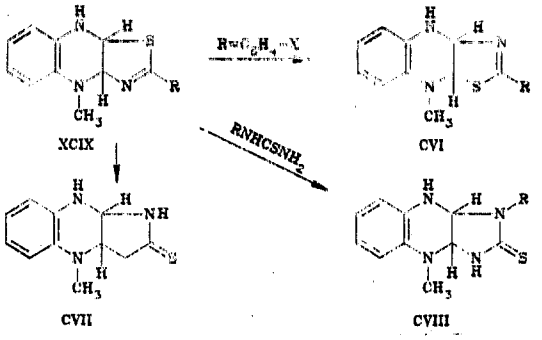
The cyclizations of the N-methylquinoxalinium ion with imido esters [108, 109] and β-keto acid amides [110], which lead in both cases to annelation of the pyrrole ring of CIV and CV, which do not have analogies in the 2,3-dichloropyrazine and quinoxaline series, have been described.



CIV XCIV CV

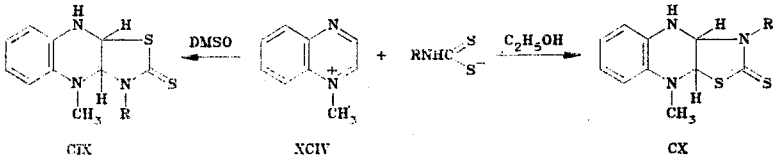
The most characteristic feature of the cyclizations of 1,4-diazinium cations with dinucleophiles is their reversibility. The ability of the resulting cycloadducts to dissociate to the starting substances, which has been demonstrated in a number of studies [109, 110, 112], creates the prerequisites for different sorts of isomerization reactions. Thus in the presence of acids thiazolo[4,5-b]quinoxalines XCIV undergo isomerization to either regioisomeric substances CVI or to pyrrolo[2,3-b]quinoxaline-2-thiones CVII, depending on the substituent [112].

In addition, in the hydrogenated quinoxaline series there is a possibility of transition from some heterocyclic systems to others that are more thermodynamically stable. Thus when thiazolo[4,5-b]-quinoxalines are heated in alcohol solution in the presence of thioureas, they are converted to the corresponding imidazo[4,5-b]-quinoxalines CVIII in high yields [112].



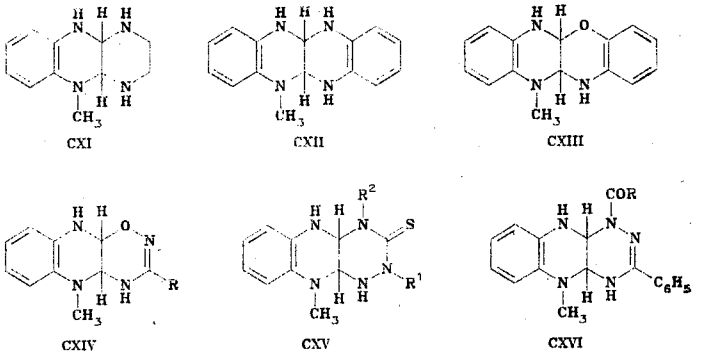
Reactions involving the isomerization of pyrrolo[2,3-b]-quinoxalines CV, in the course of which their spatial structures change, are also known [109].

Yet another peculiarity of the cyclization reactions of quinoxalinium cations with dinucleophiles in general and with N-alkyldithiocarbamates in particular is the possibility of the formation of regioisomeric cyclization products CIX and CX.



The reasons for the change in the regioorientation of the ring undergoing annelation were examined in [106, 113].

The utilization of the corresponding 1,4-dinucleophiles in cyclizations with quinoxalinium salts made it possible to develop methods for the synthesis of tetrahydroquinoxalines condensed with the most diverse six-membered heterocycles: pyrazine CXI, quinoxaline CXII, benzoxazine CXIII, and oxadiazine CXIV [114], as well as triazine CXV and CXVI [115].



The literature data examined in our review show that for cyclization reactions of azines with bifunctional nucleophiles the heteroring should have either two readily replaceable groups or increased electrophilicity, which is achieved either by the introduction of nitro or aza groups or by conversion of the azine to the cationic form.

The important preparative value of the examined cyclization reactions is clearly seen from the diversity of the substances obtained from them, many of which are biologically active.

A knowledge of the principles and peculiarities of the cyclization reactions of azines with bifunctional nucleophiles makes it possible to carry out the purposeful synthesis of new heterocyclic compounds. There is no doubt that the further study of the cyclization reactions of azines with dinucleophiles will make a contribution to the development of new methods for the synthesis of heterocyclic compounds and will have a fruitful effect on the development of theoretical concepts in the chemistry of nitrogen heterocycles.

LITERATURE CITED

1. L. D. Mashkovskii, Medicinals [in Russian], Parts 1 and 2, Meditsina, Moscow (1972).
2. A. A. Kost, Khim. Geterotsikl. Soedin., No. 9, 1200 (1980).
3. G. W. H. Cheeseman and R. F. Cookson, Condensed Pyrazines, Vols. 1 and 2, J. Wiley and Sons, New York (1979).
4. E. M. Hawes and D. G. Wibberley, J. Chem. Soc., C, No. 3, 315 (1966).
5. H. Schäfer, K. Gewald, and M. Sefert, J. Prakt. Chem., 318, 294 (1976).
6. H. Schäfer, B. Bartho, and K. Gewald, Z. Chem., 13, 39 (1973).
7. Yu. A. Sharanin and V. K. Promonenkov, Izv. Sibirsk. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk, No. 2, 80 (1980).
8. A. A. Aroyan, L. A. Grigoryan, and M. A. Kaldrikyan, Arm. Khim. Zh., 23, 148 (1980).
9. G. B. Barlin and P. Lakshrninarayama, Aust. J. Chem., 31, 389 (1978).
10. J. Wielgat and Z. Damagala, Roczn. Chem., 49, 1039 (1975).
11. A. Zayed, H. H. Zoorob, and M. T. El-Wassimi, Pharmazie, 33, 572 (1978).
12. D. Rose, West German Patent No. 2834605; Chem. Abstr., 93, 132372 (1980).
13. J. Wolinski and A. Ilezuk, Acta Bull. Pharm., 33, 547 (1976).
14. E. A. Oostven and H. C. van der Plas, Recl. Trav. Chim., 98, 441 (1979).
15. V. M. Cherkasov, G. Ya. Remennikov, A. A. Kisilenko, and E. A. Romanenko, Khim. Geterotsikl. Soedin., No. 2, 239 (1980).
16. J. V. Hay and J. F. Wolfe, J. Am. Chem. Soc., 97, 3702 (1975).
17. D. R. Carver, J. S. Hubbard, and J. F. Wolfe, J. Org. Chem., 47, 1036 (1982).
18. E. Hayashi and A. Utsunomiga, Yakagaku Zasshi, 95, 774 (1975); Chem. Abstr., 85, 183002 (1976).
19. R. K. Anderson and G. W. H. Cheeseman, J. Chem. Soc., Perkin I, No. 1, 129 (1974).
20. C. Iijima and E. Hayashi, Yakugaku Zasshi, 92, 736 (1972); Chem. Abstr., 77, 75190 (1972).
21. Y. C. Tong and H. O. Kerlinger, J. Heterocycl. Chem., 20, 365 (1983).
22. E. Matsumura and M. Ariga, Bull. Chem. Soc. Japan, 46, 3144 (1973).
23. H. Noda, T. Yamamori, M. Yoshida, and M. Hamana, Heterocycles, 4, 453 (1976).
24. E. Matsumura, M. Ariga, and Y. Tohda, Bull. Chem. Soc. Jpn., 53, 2891 (1980).
25. A. A. Prokopov and L. N. Yakhontov, USSR Inventor's Certificate No. 687075; Byull. Izobret., No. 35, 107 (1979).
26. A. A. Prokopov, L. F. Lindberg, T. F. Vlasova, Yu. N. Sheinker, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 4, 492 (1978).
27. L. N. Yakhontov, M. Ya. Uritskaya, A. A. Prokopov, V. A. Loginov, and T. F. Vlasova, Khim. Geterotsikl. Soedin., No. 10, 1428 (1975).
28. M. Ya. Uritskaya, A. A. Prokopov, and L. N. Yakhontov, USSR Inventor's Certificate No. 520364; Byull. Izobret., No. 25, 77 (1976).
29. S. D. Carter and G. W. H. Cheeseman, Tetrahedron, 34, 981 (1978).
30. I. M. Ismail and W. Sauer, Indian J. Chem., Sect. B, 16B, 683 (1978).
31. I. M. Ismail, R. Iacobi, and W. Sauer, Z. Chem., 17, 15 (1977).
32. V. K. Chadha and V. K. Saxema, J. Indian Chem. Soc., 57, 946 (1980).
33. V. K. Chadha, J. Indian Chem. Soc., 53, 1170 (1976).
34. K. S. Dhaka, J. Mohan, V. K. Chadha, and A. K. Pujari, Indian J. Chem., 12, 966 (1974).
35. A. K. El-Shafel, H. S. El-Kashef, A.-B. Ahmed, and G. Chattas, Gazz. Chim. Ital., 111, 409 (1981).
36. H. K. Pujari, Indian J. Chem., Sect B., 17B, 364 (1979).
37. K. Senda, M. Ioshiba, H. Kanazawa, and S. Nishigaki, J. Heterocycl. Chem., 19, 77 (1982).
38. C. A. Wilson and C. E. Mixan, US Patent No. 4075209; Chem. Abstr., 88, 190898 (1978).
39. D. F. Morrow, US Patent No. 4254124; Chem. Abstr., 95, 24546 (1981).
40. C. O. Okafor, Proceedings of the 8th International Congress of Heterocyclic Chemistry, Graz, Austria (1981), p. 348.
41. C. O. Okafor, J. Heterocycl. Chem., 18, 405 (1981).
42. W. S. Saari, D. W. Cochran, Y. C. Lee, E. L. Cresson, J. P. Springer, M. Williams, J. A. Totaro, and G. G. Yarbrogh, J. Med. Chem., 26, 564 (1983).
43. A. K. El-Shafei, G. Vernin, and J. Metzger, Gazz. Chim. Ital., 111, 413 (1981).
44. A. H. Gulbenk and D. J. Horne, US Patent No. 3808208; Chem. Abstr., 81, 10574 (1974).
45. C. O. Okafor, Phosphorus Sulfur, 4, 79 (1978).
46. C. O. Okafor, Eur. J. Med. Chem., 12, 249 (1977).
47. C. O. Okafor, J. Heterocycl. Chem., 17, 149 (1980).
48. C. O. Okafor, J. Org. Chem., 43, 592 (1982).
49. C. O. Okafor, I. O. Uche, and L. E. S. Akpanisi, J. Heterocycl. Chem., 18, 1589 (1981).
50. C. O. Okafor, J. Heterocycl. Chem., 17, 1587 (1980).

51. V. K. Chadha, J. Indian Chem. Soc., 55, 817 (1978).
52. K. S. Dhaka, J. Mohan, V. K. Chadha, and H. K. Pujari, Indian J. Chem., 12, 287 (1974).
53. A. J. Eliott, J. Heterocycl. Chem., 18, 799 (1981).
54. C. O. Okafor, J. Org. Chem., 38, 4386 (1973).
55. C. O. Okafor, M. L. Steenberg, and J. P. Buckley, J. Heterocycl. Chem., 12, 813 (1975).
56. R. R. Gupta, N. K. Goswami, S. K. Jain, and M. Kumar, Ann. Soc. Sci. Bruxelles, Ser. 1, 94, 219 (1980).
57. H. L. Yale and J. Bernstein, US Patent No. 3106581; Chem. Abstr., 60, 2962 (1964).
58. Y. Maki, Yakugaku Zasshi, 77, 485 (1957); Chem. Abstr., 51, 14738 (1957).
59. A. R. Gennaro, J. Org. Chem., 24, 1156 (1959).
60. H. L. Yale and F. Sowinski, J. Am. Chem. Soc., 80, 1651 (1958).
61. N. H. Kurihara and D. E. Balbitz, US Patent No. 3853901; Chem. Abstr., 82, 112084 (1975).
62. N. H. Kurihara and D. E. Balbitz, US Patent No. 3843644; Chem. Abstr., 82, 43432 (1975).
63. B. M. Sawant and T. D. Sayad, J. Shivaji Univ. Sci., 17, 63 (1977).
64. N. D. Kurihara and D. E. Balbitz, US Patent No. 3849415; Chem. Abstr., 82, 86290 (1975).
65. N. D. Kurihara and D. E. Balbitz, US Patent No. 3829425; Chem. Abstr., 81, 136155 (1974).
66. N. D. Kurihara and D. E. Balbitz, US Patent No. 3825548; Chem. Abstr., 81, 120647 (1974).
67. C. O. Okafor. J. Heterocycl. Chem., 18, No. 7, 1445 (1981).
68. C. O. Okafor, J. Heterocycl. Chem., 16, No. 5, 1025 (1979).
69. T. J. Dietsche, US Patent No. 4029657; Chem. Abstr., 87, 102381 (1977).
70. T. J. Dietsche, US Patent No. 4080499; Chem. Abstr., 89, 43506 (1978).
71. W. B. Wright, G. O. Morton, and A. S. Tomefcik, J. Heterocycl. Chem., 16, 1345 (1979).
72. Y. Ito and Y. Hamada, Chem. Pharm. Bull., 26, 1375 (1978).
73. V. A. Petrow and E. L. Rewald, J. Chem. Soc., No. 5, 313 (1945).
74. G. I. Migachev and V. A. Danilenko, Khim. Geterosikl. Soedin., No. 7, 867 (1982).
75. C. O. Okafor, J. Chem. Soc., Chem. Commun., No. 21, 878 (1974).
76. C. O. Okafor, J. Heterocycl. Chem., 13, 107 (1976).
77. C. O. Okafor, Heterocycles, 7, 391 (1977).
78. M. H. Fisher, A. E. Lusi, and J. R. Egerton, J. Pharm. Sci., 66, 1349 (1977).
79. J. C. Turley, G. E. Martin, and R. R. Inners, J. Heterocycl. Chem., 18, 1169 (1981).
80. D. E. Ames and R. J. Ward, J. Chem. Soc., Perkin I, No. 6, 534 (1975).
81. C. H. Womack, L. M. Martin, G. E. Martin, and K. Smith, J. Heterocycl. Chem., 19, 1447 (1982).
82. C. H. Womack and G. E. Martin, J. Heterocycl. Chem., 18, 1165 (1981).
83. S. R. Caldwell, G. E. Martin, S. H. Simonsen, R. R. Inners, and M. R. Willcott, J. Heterocycl. Chem., 18, 479 (1981).
84. S. R. Caldwell and G. E. Martin, J. Heterocycl. Chem., 17, 589 (1980).
85. J. S. Davies, K. Smith, J. R. Turner, and G. Gyner, Tetrahedron Lett., No. 52, 5035 (1979).
86. S. R. Caldwell, J. C. Turley, and G. E. Martin, J. Heterocycl. Chem., 17, 1153 (1980).
87. E. Berenyi, P. Benko, and L. Pallos, Acta Chim. Acad. Sci. Hung., 90, 395 (1976); Chem. Abstr., 86, 139997 (1977).
88. E. Berenyi, P. Benko, and L. Pallos, Acta Chim. Acad. Sci. Hung., 90, 395 (1976); Chem. Abstr., 86, 139998 (1977).
89. E. Berenyi, L. Pallos, L. E. Petocz, P. Benko, P. Gorog, and Z. Budai, Hungarian Patent No. 2322418; Chem. Abstr., 80, 27303 (1973).
90. P. Benko, E. Berenyi, A. Messner, G. Hejos(Hayos), and L. Pallos, Acta Chim. Acad. Sci. Hung., 90, 405 (1976); Chem. Abstr., 85, 139999 (1977).
91. P. Benko, M. D. Berenyi, A Messner, G. Hayos, and L. Pallos, Magy. Kem. Fol., 82, 183 (1976); Chem. Abstr., 85, 46593 (1976).
92. B. De Croiz, M. J. Strauss, A. De Fusco, and D. C. Palmer, J. Org. Chem., 44, 1700 (1979).
93. V. N. Charushin and O. N. Chupakhin, Usp. Khim., 53, 1648 (1984).
94. J. A. Zoltewicz, L. S. Almick, and I. K. O'Halloran, J. Org. Chem., 41, 1303 (1976).
95. J. A. Zoltewicz, T. M. Oestreich, I. K. O'Halloran, and L. S. Helmick, J. Org. Chem., 38, 1949 (1973).
96. A. Srikrishna, R. R. Readly, S. N. Rao, D. S. Iyengar, and U. T. Bhalerao, Chem. Lett., No. 4, 535 (1981).
97. A. Albert and H. Mizuno, J. Chem. Soc., Perkin I, No. 15, 1615 (1973).
98. V. N. Charushin, V. G. Baklykov, O. N. Chupakhin, N. N. Vereshchagina, L. M. Naumova, and N. N. Sorokin, Khim. Geterotsikl. Soedin., No. 12, 1684 (1983).
99. V. N. Charushin, M. G. Poinzovskii, O. N. Chupakhin, A. I. Rezvukhin, G. M. Petrova, and Yu. A. Efremov, Khim. Geterotsikl. Soedin., No. 11, 1543 (1981).
100. V. N. Charushin, O. N. Chupakhin, E. O. Sidorov, M. P. Vikhrieva, and T. P. Pastukhova, USSR Inventor's Certificate No. 691449; Byull. Izobret., No. 38, 77 (1979).

101. V. N. Charushin, I. Ya. Postovskii, and O. N. Chupakhin, Dokl. Akad. Nauk SSSR, 249, 351 (1979).
102. O. N. Chupakhin, V. N. Charushin, and Yu. V. Shnurov, Zh. Org. Khim., 16, 1064 (1980).
103. V. N. Charushin, O. N. Chupakhin, and A. I. Rezvukhin, Heterocycles, 16, 195 (1981).
104. O. N. Chupakhin, V. N. Charushin, N. A. Klyuev, A. I. Rezvukhin, and V. A. Semion, Khim. Geterotsikl. Soedin., No. 9, 1392 (1981).
105. V. G. Baklykov, V. N. Charushin, O. N. Chupakhin, and V. N. Drozd, Khim. Geterotsikl. Soedin., No. 5, 686 (1984).
106. V. N. Charushin, V. G. Baklykov, O. N. Chupakhin, G. M. Petrova, and E. O. Sidorova, Khim. Geterotsikl. Soedin., No. 5, 680 (1984).
107. L. M. Naumova, V. N. Charushin, O. N. Chupakhin, and G. G. Izmailova, Khim. Geterotsikl. Soedin., No. 3, 390 (1985).
108. O. N. Chupakhin, V. N. Charushin, and L. M. Naumova, Khim. Geterotsikl. Soedin., No. 6, 843 (1981).
109. O. N. Chupakhin, V. N. Charushin, and L. M. Naumova, Dokl. Akad. Nauk SSSR, 261, 384 (1981).
110. V. N. Charushin, L. M. Naumova, G. G. Izmailova, and O. N. Chupakhin, Khim. Geterotsikl. Soedin., No. 8, 1120 (1983).
111. M. G. Ponizovskii, O. N. Chupakhin, V. N. Charushin, and G. G. Aleksandrov, Khim. Geterotsikl. Soedin., No. 10, 1410 (1982).
112. V. N. Charushin, V. G. Baklykov, O. N. Chupakhin, and V. N. Drozd, Khim. Geterotsikl. Soedin., No. 3, 396 (1985).
113. V. N. Charushin, M. G. Ponizovskii, O. N. Chupakhin, E. O. Sidorov, and I. M. Sosonkin, Khim. Geterotsikl. Soedin., No. 5, 669 (1985).
114. O. N. Chupakhin, V. N. Charushin, M. G. Ponizovskii, and L. M. Naumova, Khim. Geterotsikl. Soedin., No. 5, 706 (1984).
115. V. N. Charushin, V. G. Baklykov, O. N. Chupakhin, and L. M. Naumova, Khim. Geterotsikl. Soedin., No. 9, 1284 (1984).

SYNTHESIS OF 2-AMINO-4,5-DISUBSTITUTED 3,5-DICYANO-4,5-DIHYDROFURANS

O. E. Nasakin, E. G. Nikolaev,
P. B. Terent'ev, A. Kh. Bulai, and
A. G. Kalandarishvili

UDC 547.447'724.07

A new reaction was found for the preparation of difficult-to-obtain polyfunctional dihydrofurans, viz., the reaction of tetracyanoethylated ketones with hydrogen peroxide in the presence of a base.

Continuing our research on the synthesis and chemistry of tetracyanoethylated ketones [1, 2] we studied the reaction of tetracyanoethylated ketones Ia-e with hydrogen peroxide in an alkaline medium under the conditions of the Radzishevskii reaction [3, 4]. It is known that this reaction proceeds with the formation of acid amides from carboxylic acid nitriles; it is insensitive to the radicals or functional groups in the starting nitrile. Thus, for example, malonic acid dinitrile forms malonitrile monoamide with hydrogen peroxide [5].

We noted a vigorous reaction in alcohol solutions of tetracyanoethylated ketones I with hydrogen peroxide and the attendant liberation of gases, which were identified as hydrocyanic acid and carbon dioxide. When we carried out the same reaction in an aqueous solution of a base, viz., potassium bicarbonate (tetracyanoethylated ketones I decompose in

I. N. Ul'yranov Chuvash State University, Cheboksary 428015. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1027-1030, August, 1985. Original article submitted May 10, 1984.

