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CHEMISTRY OF HETEROCYCLIC COMPOUNDS AT THE INSTITUTE OF ORGANIC CHEMISTRY, NATIONAL ACADEMY OF SCIENCES OF UKRAINE (REVIEW)

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The present work is dedicated to the 70th anniversary of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. It contains a review of achievements in the chemistry of heterocyclic compounds, a brief historical account, and information on the work of the Institute's team in recent years.

Keywords: benzimidazoles, benzothiazoles, indolenines, pyrans, thiopyrans, phenazines, cyanine dyes.

At the Institute of Organic Chemistry, National Academy of Sciences of Ukraine, since its creation in 1939 systematic investigations have been carried out on various heterocyclic systems that are of theoretical interest and are promising for use in various branches of science, medicine, industry, and agriculture.

Chemistry of Phenazine

The subject matter of investigations by A. I. Kiprianov (1896-1972) and his collaborators embraced, in addition to cyanine dyes, a series of related fields of organic chemistry such as the synthesis and investigation of new heterocyclic compounds and in particular intermediate products in the synthesis of dyes. One direction in the investigations developed by Kiprianov in the post-war period was the establishment of a relation between the structure of heterocyclic compounds and their physiological activity. This scientific direction covered a wide range of aspects of the chemistry of phenazine, benzothiazole, and pyridothiazoles. The work essentially involved establishment of the structure of certain natural antibiotics, the search for new physiologically active substances, and the synthesis of new medical products. In 1947 under the leadership of Kiprianov investigations were started on the chemistry of phenazine (S. B. Serebryanyi, E. S. Rozum, V. P. Chernetskii) [1]. The Wohl–Aue alkaline condensation of aromatic nitro compounds with aromatic amines was widely used for the synthesis

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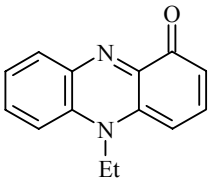
of phenazine derivatives. The alkyl- and alkoxyphenazines, halo- and trifluoromethylphenazines and their N-oxides, and a series of other derivatives of phenazine were synthesized. As a result of these investigations a method was developed for the synthesis of sanazine (10-ethylphenazin-1-one) (**1**) [2] a homolog of the natural antibiotic pyocyanin (10-methylphenazin-1-one). Sanazine underwent extensive clinical trials and found use for the treatment of certain forms of tuberculosis.

The most important achievements in this part of the investigations were the establishment of the structure and the synthesis of 1,6-dihydroxyphenazine 5,10-dioxide (**2**) – the natural antibiotic iodinine – realized by S. B. Serebryanyi, V. P. Chernetskii, and A. I. Kiprianov in 1950 [3, 4]. This was the first synthesis of an antibiotic performed in the USSR.



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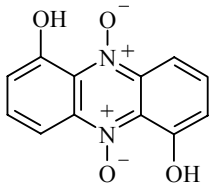
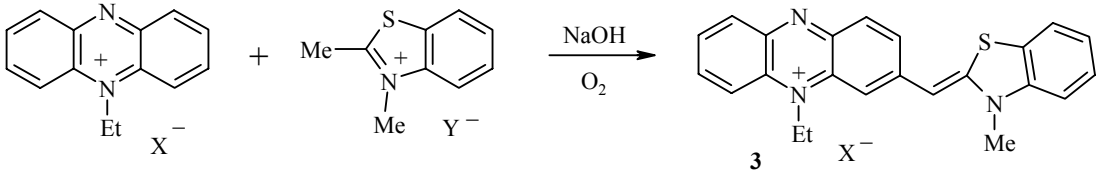


2

The nucleophilic substitution reactions of phenazinium salts – the amination of alkylphenazinium salts, their condensation with ketomethylene compounds and with quaternary salts of nitrogen heterocycles – have been widely investigated. Cyanine dyes, phenazine derivatives such as the dye **3**, were obtained [5].



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A considerable number of researches starting from 9,10-diacetyldihydrophenazine were carried out. In its properties it is a typical aromatic compound that is easily nitrated and on chloronation gives mono- and dichloro derivatives where the substituent is directed to the β-position. A method was developed in this way for the preparation of 2-nitro- and 2-aminophenazines.

Synthesis of Heterocyclic Compounds for the Production Cyanine Dyes

The work of Kiprianov and his collaborators on the synthesis of cyanine dyes led to significant developments in the chemistry of the necessary heterocyclic compounds [6].

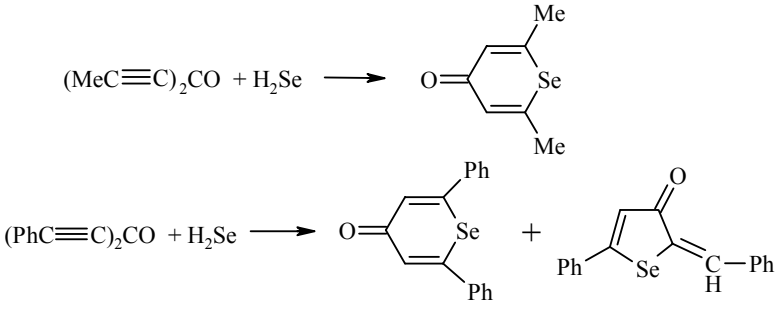
E. D. Sych developed original methods for the synthesis of many derivatives of thiazole and its quaternary salts [7]. 2-Methylbenzothiazoles with various substituents in the benzene ring were synthesized (E. D. Sych, I. K. Ushenko) [7-10]. Benzimidazoles with various substituents, including heterocyclic substituents, were obtained (V. M. Zubarovskii) [11-15]. Pyridines and quinolines containing substituents with triple bonds at positions 2 and 4 and used for the production of dyes were obtained (G. G. Dyadyusha) [16]. 2-Vinylbenzothiazole and other benzothiazoles containing substituents with double bonds at position 2 were obtained, and the addition of nucleophilic reagents to them was investigated (A. Ya. Ilchenko) [17].

New trinuclear condensed heterocycles were obtained: Thiazoloquinoxalines, triazolo-, pyrazolo-, and imidazobenzothiazoles (S. G. Fridman) [18]. Systematic investigations were carried out in the field of condensed nitrogen-containing heterocycles – benzobisthiazoles, benzobisoxazoles, benzodipyrrolenines. Heterocyclic analogs of *p*-dimethylaminobenzaldehyde in the furan, thiophene, and selenophene series were obtained (F. A. Mikhailenko) [19].

Certain condensed heterocycles containing a thiazole ring, such as thiazolopyridines, and also mesoionic nitrogen-containing heterocycles were obtained (N. N. Romanov) [20]. It was shown that mesoionic condensed nitrogen-containing heterocycles are formed during the reaction of α-aminoazoles where there is no tautomerism between the endo- and exocyclic nitrogen atoms with ω-bromoacetophenones (A. G. Maidannik) [21].

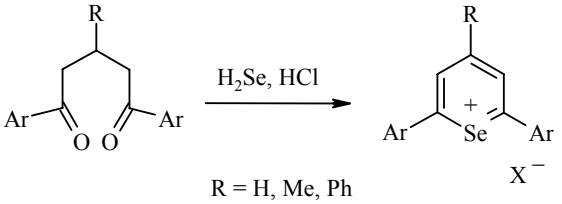
Investigations in the Field of Pyrones, Pyrylium Salts, and their Thio and Seleno Analogs and Benzo Homologs

In the sixties polymethine dyes based on pyrylium salts and their hetero analogs remained little investigated although new color relationships and also useful properties for a series of new technologies and primarily laser technology could be expected from their study. The oxygen- and sulfur-containing six-membered heterocycles themselves also were not studied systematically. Analogous derivatives of selenium were practically unknown. Investigations were carried out by A. I. Tolmachev and co-authors on the synthesis and chemical and physicochemical properties of pyrones and pyrylium salts and their hetero analogs for the purpose of further use of compounds of this type in the synthesis of polymethine dyes. It was found that dipropynyl ketones in the presence of basic catalysts are capable of adding hydrogen selenide with the formation of derivatives of the previously unknown heterocyclic 1-seleno-γ-pyrone system. In the case of 3,5-heptadiyn-4-one 2,6-dimethyl-1-seleno-γ-pyrone is formed with a high yield. In the case of 1,5-diphenyl-1,4-pentadiyn-3-one 2-benzylidene-3-oxo-5-phenyl-2,3-dihydroselenophene is also formed at the same time as 2,6-diphenyl-1-seleno-γ-pyrone [22].



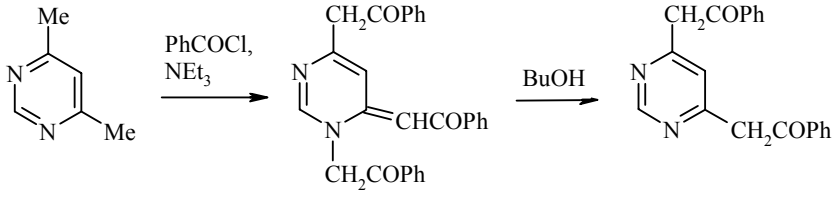
A general method was found for the production of previously unknown 2,6-diaryl-, 2,4,6-triaryl-, and 4-alkyl-2,6-diaryl-substituted selenopyrylium salts, involving treatment of substituted pentanediones with a mixture of hydrogen selenide and hydrochloric acid [23].

The ^{1}H NMR spectra, electronic structure, and basicity of 2- and 4-pyrones and thio- and selenopyrones and their reactivity [24-28] and also the reactivity of pyrylium and benzopyrylium salts [29-31] were studied.



Chemistry of Pyrimidines and Purines

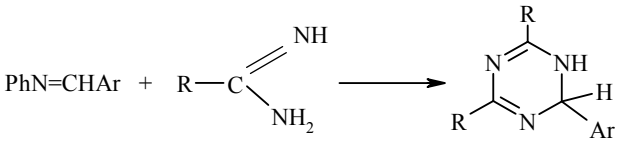
A cycle of researches on the chemistry of pyrimidine and purines was carried out under the leadership of V. M. Cherkasov. The reaction of the active methyl groups of methylpyrimidines with carboxylic acid chlorides was investigated for the first time [32].



A new type of ketone of the pyrimidine series was obtained, and their tautomerism was studied. The activity of the methyl groups in methylpyrimidines was also studied in reaction with dimethyl formamide dimethyl acetal. Reactive enamines of the pyrimidine series (dimethylaminovinylpyrimidines) were synthesized, and new pyrimidine derivatives were obtained on their basis: Ketones, thioamides, substituted pyrimidinylacetic acids.

Standards of cytokinin activity – kinetin (6-furfurylaminopurine or furfuryladenine) and 6-benzylaminopurine – and new types of cytokinins (phytohormones) were obtained for the first time in the USSR. Among the latter compounds more active than the standards were found [33]. Factors influencing the direction of the reactions and the yields of the respective purines were established as a result of studying the cyclization of aminopyrimidines (L. K. Kurilenko) [34].

The reaction of the amidines of carboxylic acids with aldehydes was investigated. The reaction takes place with the formation of 1,2-dihydro-*sym*-triazines according to a diene synthesis mechanism. This method was first used for the production of pyrimidine compounds. The transamination of azomethines and ketimines with the amidines of carboxylic acids, also resulting in the formation of 1,2-dihydro-*sym*-triazines, was discovered [35].



R = Ph, CCl_3, CF_3; Ar = Ph, *p*-ClC_6H_4, *p*-$Me_2NC_6H_4$

A new type of heterylformazan (unsymmetrical pyrimidinylarylformazans and symmetrical pyrimidinyl-2-formazans) was obtained. A diene synthesis was realized with formazans containing a 1,2,4-aza-1,3-diene fragment and in reaction of 1,4-cycloaddition with acetylenedicarboxylic ester led to derivatives of 1,4-dihydro-1,2,4-triazines (I. A. Nasyr) [36]. Thiacyclophanes of the pyrimidine series were synthesized (T. A. Dashevskaya) [37], and N,N-diphenylhydrazinopyrimidines were synthesized as leuco bases of free radicals (analogs of diphenylpicrylhydrazine containing pyrimidine rings). Pyrimidinyl isocyanates, pyrimidinyloxamoyl chlorides, and their transformation products were obtained in the reaction of oxalyl chloride with aminopyrimidines (I. V. Boldyrev) [38].

Stable anionic σ-complexes were synthesized from 5-nitropyrimidines with the anions of acetone and acetophenone. It was shown that during recyclization the pyrimidine ring is transformed by the action of carbanions and strong bases into derivatives of pyridine and benzene. The alkylation of anionic σ-complexes of the pyrimidine series leads to the formation of a new type of dihydropyrimidines containing nitro and alkyl groups at position 5, which are oxidized to difficultly obtainable 5-alkylpyrimidines (G. Ya. Remennikov) [39].

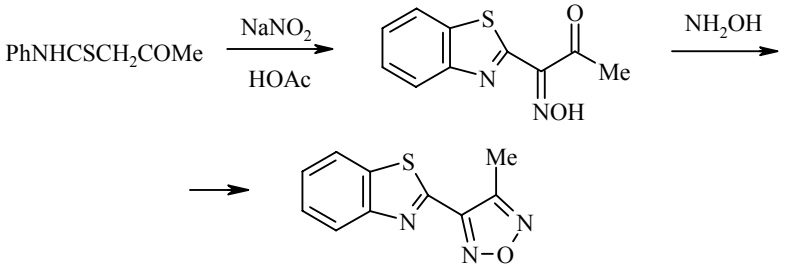
New Transformations of Thioamides with an Active Methylene Group to Derivatives of Nitrogen-Containing Heterocycles

In the 1960s P. S. Pelkis and his co-workers (R. G. Dubenko, V. M. Neplyuev, A. N. Borisevich, A. D. Grabenko) showed that the thiocarbamoylation of the sodium derivatives of compounds containing an

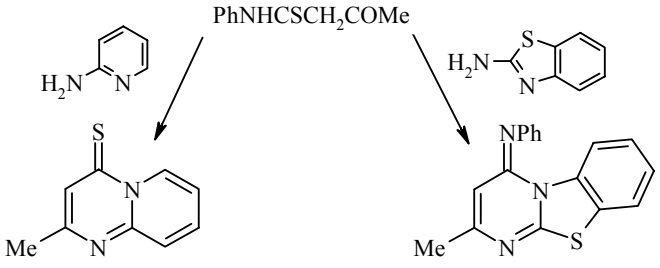
active methylene group (e.g., cyanoacetic ester [40], acetylacetone [41], (arylsulfonyl)acetyl(cyano)methanes [42, 43]) with aryl isothiocyanates provides a general method for the synthesis of functionalized thioacetamides with various structures. It was established that these thioamides are polyfunctional compounds capable of entering into reaction both with electrophiles and with nucleophiles. This gave rise to the widespread use of these reagents in the synthesis of various heterocycles.

Under the guidance of M. O. Lozinskii A. N. Borisevich first obtained N-aryl-3-oxo(thioxo)-2-phenylaminomethylenebutanethioamides and studied their condensation and cyclization to derivatives of pyrazole (with derivatives of hydrazine), 1,2,4,5-*sym*-tetrazine (with hydrazine hydrate), and pyrimidine (with guanidine carbonate). Substituted derivatives of the new condensed heterocyclic system pyrazolo[3,4-*c*]pyrimidine were obtained by this method. The reactions of N-aryl-3-oxobutanethioamides with α-halo ketones and ethyl chloroacetate, leading to the formation of 3-acetyl-5-acyl-5-(alkanoyl)aroyl-2-arylaminothiophenes and derivatives of 3-acetyl-2-arylamino-5-ethoxycarbonylthiophenes, were investigated [44].

It was found that together with hydroxyimination of the active methylene groups the nitrosation of N-aryl-3-oxobutanethioamides with sodium nitrite in acetic acid leads to simultaneous heterocyclization of the thioarylamide groups. The products are 1-(6-R-benzothiazol-2-yl)-1-hydroxyimino-2-propanones, which are starting compounds for the synthesis of little studied derivatives of 1,2,5-oxadiazole [45].

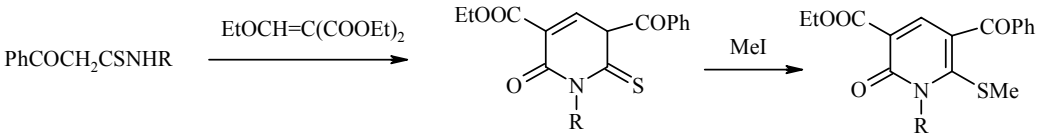


V. N. Britsun in collaboration with A. N. Borisevich and M. O. Lozinskii investigated the regioselectivity of the cyclization of N-aryl-3-oxobutanethioamides with heterocyclic nitrogen-containing 1,3-dinucleophiles [46-49] and showed that the isomeric N-aryl-3-oxobutanethioamides and N-alkyl-3-aryl-3-oxobutanethioamides undergo self-condensation to 1-alkyl-5-(N-alkylaminothiocarbonyl)-4,6-diaryl-1,2-dihydropyridine-2-thiones [47, 50].



Together with analytical chemists of the Chemical Faculty at T. G. Shevchenko Kiev University under the guidance of V. M. Zaitsev the pK_a values of thioamides with an active methylene group (R^1N,R^2N-3-oxopropanethioamides, 2-arylsulfonylthioacetamides, 2-cyanoacetamides) were measured by pH-metric titration [51], and their cycloacylation with 3-aryl-2-propenoyl chlorides was investigated [52, 53]. It was found that the reaction products were derivatives of 6-thioxopiperidin-2-one, 2,3-dihydro-4H-thiopyran-4-one, and dihydro-4H-1,3-thiazin-4-one. The relationships governing these cyclocondensations were analyzed

and classified in [54]. On the basis of previous investigations a procedure was developed for the synthesis of 5-benzoyl-3-ethoxycarbonyl-6-methylthiodihydropyridin-2-ones from available starting compounds – 3-oxopropanethioamides and diethyl ethoxymethylenemalonate [55].



It was first shown that 5-benzoyl-3-ethoxycarbonyl-6-methylthiodihydropyridin-2-ones react selectively with heterocyclic nitrogen-containing 1,3-dinucleophiles to form a series of condensed polycyclic heterosystems, including new pyrido[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidines, pyrazolo[1,5-*a*]pyrido[2,3-*d*]-pyrimidines, pyrido[2,3-*d*]pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidines, 5H-pyrido[2,3-*d*]thiazolo[3,2-*a*]pyrimidines, and benzo[4,5]imidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidines. It was found that 5-benzoyl-3-ethoxycarbonyl-6-methylthiodihydropyridin-2-ones react with nitrogen-containing 1,4-dinucleophiles – *ortho*-phenylenediamine, *ortho*-aminothiophenol, and ethylenediamine. The reaction takes place as recyclization with the formation of derivatives of 3-(imidazol-2'-yl)-2-pyranone. The reaction of 5-benzoyl-3-ethoxycarbonyl-6-methylthiodihydropyridin-2-one with the 1,5-dinucleophile 1,3-diaminopropane takes place in a similar direction [46-49]. Thus, a new recyclization that is general in nature and can be used as a preparative method for the synthesis of previously unknown derivatives of 2-pyranone was discovered.

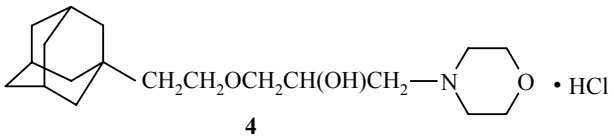
Syntheses of Biologically Active Heterocycles

One method for the synthesis of the above-mentioned compounds is the cycloacylation of thioamides with derivatives of unsaturated carboxylic acids – acetylenedicarboxylic ester, maleic anhydride, propiolic esters, etc. [56]. V. N. Britsun, A. N. Esipenko, and M. O. Lozinskii showed for the first time that 3-aryl-2-propenoyl chlorides can be used for the cycloacylation of thioamides [57-59] and established that this reaction can be general in nature and takes place both with acyclic and with cyclic derivatives of thiourea with the formation of N-acylthioureas and derivatives of 2,3,5,6-tetrahydro-4H-1,3-thiazin-4-one [60].

Advantages of the methods developed for the synthesis of derivatives of 4H-1,3-thiazin-4-one are the availability of the starting compounds, the single-stage nature of the synthesis, the technological expediency of the experiment, the high yields (67-82%), and the possibility of wide variation of the substituents at position 6 of the thiazine ring. The last factor is of considerable importance in the search for biologically active compounds.

Trials for antimicrobial activity showed that 2-aryl-2,3-dihydro-4H-[1,3]thiazino[3,2-*a*]benzimidazol-4-ones are compounds with low toxicity (in trials with white mice LD_{50} was 3200-3890 mg/kg) and exhibit high bactericidal activity (at the level of the standards – cephtazidim, cephoperazone, and ampicillin) against staphylococcus aureus (*S. aureus*) and staphylococcus pyocyaneus (*E. coli*) [61]. Compounds of this class exhibited significant herbicidal activity against monocotyledonous plants [62].

A group of previously uninvestigated biologically active derivatives of 1-alkoxy-3-dialkylamino-2-propanol, exhibiting uterostimulant activity, was obtained for the first time (Yu. V. Korotkii, M. O. Lozinskii) [63-66]. A new method was proposed for the production of 1-alkoxy-3-dialkylamino-2-propanol by the reaction of 1-dialkylamino-2,3-epoxypropane with primary and secondary alcohols in the presence of Lewis acids ($SnCl_4$, $BF_3 \cdot Et_2O$). A series of compounds having uterostimulant activity was found as a result of modification of the structure of β-adrenergic blockers. A new original uterostimulating product ademol (1-adamantylethoxy-3-morpholino-2-propanol hydrochloride) (**4**) was synthesized. Ademol also exhibits analgesic, tranquillizing, and nootropic effects, which distinguishes it favorably from other uterotropic agents. Ademol can potentially be used for the treatment of Alzheimer's disease [64].



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Ademol exhibits clearly defined concurrent antagonism with respect to β-adrenomimetics, which is of fundamental importance in the complex therapy of childbirth. In spite of the fact that ademol is a structural analog of anapriline it has practically no effect on cardiovascular activity. It was established that ademol has some β-adrenergic blocking activity and cholinomimetic effect. Ademol is registered in Ukraine, and its use in the stimulation of birth activity is permitted.

New quaternary salts of adamantane-containing alkoxyaminopropanols, which exhibited significant antimicrobial activity and surpassed the familiar products ofloxacin, fluconazole, and amphotericin in their activity, were synthesized [63-66].

Syntheses of Sulfonyl-Containing Heterocycles

Various derivatives of methylenebis(sulfonylacetic) acid have been used for the synthesis of sulfonyl-containing heterocyclic compounds [67, 68]. Thus, the dinitrile of methylenebis(sulfonylacetic) acid reacts with ethyl formate with the formation of the products from substitution of C(1) and C(5) or C(1), C(3), and C(5).

7-Amino-3-R^1-8-(R^2-sulfonyl)-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazin-4-ones (the first representatives of geminal sulfones in which the heterocyclic rings are attached directly to the sulfur atoms of the sulfonyl groups) were synthesized by the reaction of arylsulfonylacetonitriles and the dinitriles of sulfonyldiacetic and methylenebis(sulfonylacetic) acids with 4-amino-3-methylthio-5-oxo-6-R-4,5-dihydro-1,2,4-triazines [69].

Arylhydrazonoyl Chlorides of Glyoxylic and Oxalic Acids and Arylhydrazones of Ethyl Bromoacetylglyoxylate in the Synthesis of Heterocycles

S. N. Kukota, V. N. Bodnar, M. O. Lozinskii, and co-workers developed accessible methods for the production of arylhydrazonoyl chlorides of glyoxylic and oxalic acids and arylhydrazones of ethyl bromoacetylglyoxylate and realized their heterocyclization, making it possible to obtain many nitrogen- and sulfur-containing heterocyclic compounds, including those containing various functional groups: amino, azido, iso(thio)cyanate, hydrazino, etc. [70-72].

The types of compounds named above are important synthons for the production of various types of substituted heterocycles, including Δ-1,3,4-oxadiazolone, 1,2,4,5-tetrazine [73], quinoline, tetrazole, 4-thiazolidone, pyrazolone, imidazole, 1,2,4-triazole, 8-triazinone, azetidine, imidazo[1,2-*a*]pyridine, imidazo[2,1-*a*]benzothiazole [74], 2,3-dihydro-1,4-benzothiazin-2-one, 2,3-dihydro-1,4-benzoselenazinone, imidazo[2,1-*b*]benzothiazole [74], and thiazolo[3,2-*a*]benzimidazole [74].

New derivatives of oxadiazole, thiazolidone, 8-triazinone, [3,2-*a*]benzimidazothiazole, and [3,2-*b*]benzo-thiazoloimidazole with the residues of the arylhydrazones of ethyl glyoxylate and arylhydrazonochloroformyl were obtained. Original few-stage methods were proposed for the synthesis of difficultly obtainable heterocyclic systems of thiopyrano[2,3-*d*]pyrimidine, 2,2'-substituted derivatives of 1,4-benzothiazin-2-one, pyridazolo[3,4-*a*]pyrimidine, and 5-aryl-5,6,7H-1,2,4-triazolo[1,3]thiazin-7-ones. New original directions were found for the heterocyclization of the arylhydrazones of ethyl bromoacetylglyoxylate to condensed heterocyclic systems of thiazolobenzimidazole and new substituted derivatives of thiazole and oxathiolane [73, 74].

Aryliminooxaloyl and Diaryliminodichloromalonoyl Chlorides in the Synthesis of Heterocycles

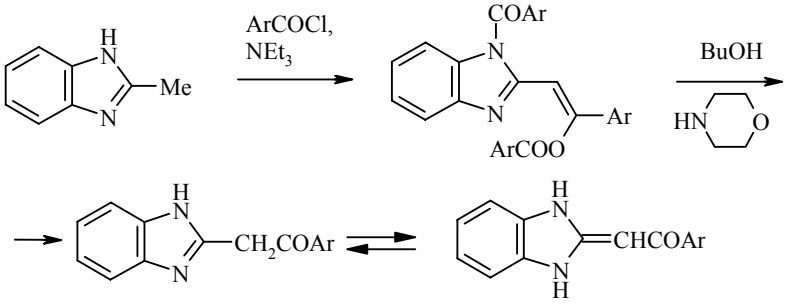
In works by O. V. Dashkovskaya and A. F. Shivanyuk under the guidance of M. O. Lozinskii methods were developed for the production of the chlorides of monoarylamides of oxalic acid and the dichlorides of monoarylphenyliminooxalic acid. Their nucleophilic exchange reactions with further chemical transformations to five-membered O,S,N-containing heterocyclic compounds with various structures, including substituted 1,3-diazetidinediones, 2,4-derivatives of Δ^4-thiazoline, imidazo[1,2-*a*]benzimidazole, imidazo[2,1-*b*]benzothiazole, and 1-thiazolo[3,2-*a*]benzimidazole, tetrazole, 2,4,6-trioxohexahydro-1,3,5-*s*-triazine, and 2-oxo-3-phenylamino-5,6-dihydro-1,4-oxazine were studied [75-77].

Bisarylimidoyl chlorides of dichloromalonic acid were synthesized for the first time [77]. Through the presence of the three reaction centers they provide convenient synthons for the production of a whole series of chemical compounds – substituted phosphonic acids of quinoline, 3,5-diarylimino-4-chloropyrazole, bis(1-aryl-5-tetrazolyl)dichloromethanes or their imino derivatives, and new substituted CH acids. With 4-arylimino-2,3-dichloroquinoline (an intermediate product in the reaction of bisarylimidoyl chloride of dichloromalonic acid) the new heterocyclic system 9,14-dihydrotetrazolo[1',5':1,2]quinolino[3,4-*b*]quinoxaline was synthesized. A method was proposed for the production of 7-substituted 2-chloro-2-ethoxycarbonyl-2H-1,4-benzothiazin-3(4H)-ones, and their reactions with nucleophilic agents were investigated. The chemical transformations of these compounds were studied, and new spiro compounds – 7-substituted 3-hydroxy-2,3-dihydro-1,4-benzothiazine-2-spiro-4-(2-oxo-1'-R-phenylimidazolidin-5-ones) – were obtained [78].

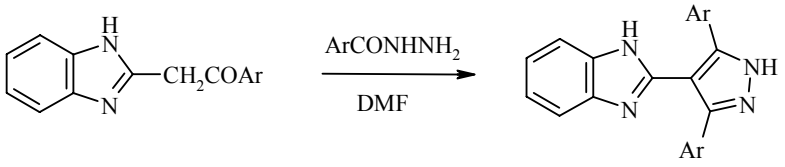
Heterocyclizations Based on 2-Phenacylidene-2,3-dihydro-1H-benzimidazoles and their Structural Analogs

M. O. Lozinskii, I. B. Dzvinchuk, and O. V. Vypirailenko realized various heterocyclizations and recyclizations based on 2-phenacylidene-2,3-dihydro-1H-benzimidazole (PDBI) and its structural analogs [79-82].

A new method was developed for the synthesis of PDBI. At the first stage 2-methylbenzimidazole was acylated with aroyl chlorides in the presence of triethylamine. At the second the obtained products were deacylated by heating with 1-butanol or morpholine. The overall yield of the PDBI was 60-89%.



With substituted hydrazines PDBI forms the corresponding alkyl-, aryl-, and aroylhydrazones. The reaction of PDBI with phenylhydrazine with heating in trifluoroacetic acid does not stop at the formation of the phenylhydrazone but is easily accompanied by indolization according to the scheme of the Fischer reaction with the formation of 2-(2-arylindol-3-yl)-1H-benzimidazoles. The reaction of PDBI with aroylhydrazines at 200°C takes place through the aroylhydrazones, which undergo cyclization to 2-(3,5-diarylpyrazol-4-yl)-1H-benzimidazoles.



The benzoylhydrazones obtained from PDBI are effective in the synthesis of 2-(1,2,3-thiadiazol-5-yl)- and 2-(3-arylpyrazol-4-yl)-1H-benzimidazoles. The former are formed during the reaction with thionyl chloride, and the latter with dimethyl formamide dimethyl acetal.

The three-component cyclocondensation of PDBI with aromatic aldehydes and urea according to the Biginelli reaction takes place in hydrochloric acid solution and gives 6-substituted 4-aryl-5-(2-benzimidazolyl)-2-oxo-1,2,3,4-tetrahydropyrimidines.

The oxidative cyclocondensation of PDBI with *o*-aminothiophenol is accompanied by isomerization and gives 3-aryl-2-(2-benzimidazolyl)-4H-1,4-benzothiazines and/or their isomeric 2H-1,4-benzothiazines.

PDBIs are suitable for the synthesis of functionalized pyrido[1,2-*a*]benzimidazoles. Thus, 1-amino-3-aryl-2-cyano-, 4-aroyl-1-aryl-2-(benzimidazol-2-yl)-, and 1-amino-4-aroyl-2-cyanopyrido[1,2-*a*]benzimidazoles and N-(3-aryl-4-benzoyl-2-oxo-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazol-2-yl)benzamides respectively are formed in the cyclocondensation reactions with malononitrile, trimethyl orthoformate, ethoxymethylenemalononitrile, and azalactones.

The alkylation of the potassium salts of PDBI leads to 1,4-diaryl-2-(2-benzimidazolyl)butane-1,4-diones. These products readily undergo cyclization when heated with hydrochloric acid with the formation of 2-(1,5-diaryl-3-furyl)-1H-benzimidazoles, and with hydrazine hydrate they give 2-(3,6-diaryl-2,5-dihydropyridazin-4-yl)-1H-benzimidazoles, which are readily oxidized to 2-(3,6-diarylpyridazin-4-yl)-1H-benzimidazoles by the action of nitrous acid.

During the investigation of PDBI and of the compounds obtained from them several new methods of heterocyclization that do not have direct analogies in the chemistry of heterocyclic compounds were discovered and studied. Thus, a new approach to the synthesis of compounds with a γ-unsubstituted pyridine ring was proposed. It is based on the familiar Hantsch reaction with the formation of 1,4-dihydropyridines. It was found that its typical three-component cyclocondensation takes place atypically if 4-(dimethylamino)benzaldehyde is used as aldehyde component and the reaction is carried out in boiling acetic acid. Under such conditions the formation of compounds with a 4-(4-dimethylaminophenyl)-1,4-dihydropyridine ring is accompanied by aromatization with cleavage of N,N-dimethylaniline, leading to compounds with a γ-unsubstituted pyridine ring. In this reaction PDBI, its structural analogs (in which the heterocycle is represented by a benzothiazole, quinoline, 1-methylbenzimidazole, or imidazole ring) and cyclohexane-1,3-diones can be used as methylenecarbonyl component. 3,5-Dimethoxyaniline, 6-amino-1,3-dimethylpyrimidine-2,4-dione, 5-amino-3-methyl-1-phenylpyrazole, and methyl β-aminocrotonate are suitable as 1,3-N,C-dinucleophile. The relationships governing the reaction and the mechanism of aromatization, which takes place as a result of dearylation, were established. As a result a convenient and general preparative method was developed for the synthesis of γ-unsubstituted functionalized compounds of pyridine, including those condensed with other rings (quinolines, acridines, pyrido[2,3-*d*]pyrimidines, pyrazolo[3,4-*b*]pyridines).

On the basis of the reaction of the initial hydrazones with aroyl chlorides, carboxylic acids, and DMF at elevated temperatures (150-200°C) an effective method was developed for the synthesis of 1-(5-arylpyrazol-3-yl)benzimidazoles. It was found that the hydrazinolysis recyclization of the structural analog of PDBI 2-phenacylidene-2,3-dihydrobenzothiazole takes place significantly more readily without acylating agents and leads to 1,9-dihydropyrazolo[4,3-*b*][1,4]benzothiazine.

It was found that the recyclization of N-monosubstituted hydrazones of 2-phenacyl-1H-benzimidazoles is initiated by acylating reagents. The reaction is promoted by increased electrophilicity of the acylating

reagent, and it takes place under the influence of the chlorides and anhydrides of carboxylic acids. Recyclization with initiation by trifluoroacetic anhydride leads to 5-(*o*-trifluoroacetoaminoanilino)pyrazoles.

Thus, it was found that PDBIs are accessible and effective polyfunctional and multipurpose reagents [79-82]. They are suitable for the synthesis of new heterocyclic compounds of many types.

The Chemistry of Partly Hydrogenated Azines

Advances in the chemistry of functionally 1-substituted heterocumulenes were used for the synthesis of partially hydrogenated derivatives of 1,3-azines (pyrimidines, 1,3-oxazines, 1,3-thiazines). New intramolecular cyclizations of 1-(imidoylthio)alkylheterocumulenes, forming the basis of the creation of methods for the synthesis of previously unknown types of 6-alkylidene- or 6-imino-functionalized 1,3,5-thiadiazines, mesoionic 2H-1,3,5-thiadiazin-5-io-4-olates, 1,3,5-thiadiazinio[2,3-*b*]benzoxazolinium perchlorates, and also the first representative of N,S-containing four-membered heteryl isothiocyanates – 3-(1-adamantyl)-2-isocyanato-2-trichloromethyl-1,3-thiazetidine [83, 84].

An original approach was found to the synthesis of new types of five- and seven-membered heterocycles with an exocyclic heterocumulene group – 2-isocyanato-1,3-benzodithio(oxothio)lanes and 2-isocyanato-1,3-benzodithiepines, which was based on the previously unknown principle of intramolecular contraction of the seven- and nine-membered heterocycles [84].

A. V. Bolbut and M. V. Vovk studied the intramolecular cyclization of the structural isomers of 1-functionalized alkylheterocumulenes – N-alkylidenecarbamates and N-alkylideneureas, which is realized as a result of the reaction of electrophilic azomethine or carbonyl groups with aromatic (heteroaromatic) rings with the formation of a new carbon–carbon bond [84].

A new reaction was found for the thermal cyclization of N-alkylidene-O-arylcarbamates and N-alkylidene-N'-arylureas, in which the aromatic ring performs the function of C-nucleophilic component. The role of the conditions and the structural factors that control its occurrence was established, the limits of its synthetic application were determined, and the most probable schemes for the cyclizations were proposed [85].

Methods were developed for the production of new pertially hydrogenated trifluoromethyl-substituted benzo[1,3]oxazinones, naphtho[1,3]oxazinones, quinazolinones, and benzoquinazolinones. It was shown that the reactions of 2-trihalomethyl-2H-1,3-benzoxazolin-2-ones with nucleophilic reagents are convenient methods for the synthesis of their new derivatives [85].

A noncatalytic intramolecular acylation of the benzene ring by carbodiimide groups was discovered for the imino analogs of the intermediates in the cyclization of N-alkylidene-O-arylcarbamates – N-(1-aroxy-2,2,2-trifluoroethyl)-N'-arylcarbodiimides. It was found that the factor controlling the realization of attack by the carbodiimide group on the aroxyl fragment is the nucleophilicity of the latter. The obtained experimental results showed that only the carbodiimides containing electron-donating substituents at position 3 of the phenyl group undergo cyclization. On the basis of the given reaction a method was developed for the synthesis of new types of 4-N-arylamino-2-trifluoromethyl-2,3-dihydro-4H-benzo[1,3]oxazines [85].

A method was proposed for the synthesis of N-aryl(heteryl)-N'-methoxycarbonyltrihaloacetamidines based on the reaction of aryl(heteryl)amines with N-(1-chloro-2,2,2-trihalo)ethylidene-O-methylcarbamates. A preparatively convenient general approach to partly hydrogenated trihalomethyl-containing pyrimidine systems was developed on the basis of the ability of N-aryl(heteryl)-N'-methoxycarbonyltrihaloacetamidines to undergo intramolecular interaction on account of electrophilic attack by the methoxycarbonyl group on the aryl (heteryl) substituent, performing the function of C-nucleophilic component. Trihalomethyl-substituted benzo[*h*]- and benzo[*f*]quinazolinones were obtained by the cyclization of N-naphthyl-N'-methoxycarbonyltrihaloacetamidines. In turn, new derivatives of furo[2,3-*d*]pyrimidin-4-ones, thieno[2,3-*d*]pyrimidin-4-ones, and isoxazolo[5,4-*d*]pyrimidin-4-ones respectively with the trihalomethyl group at position 2 of the pyrimidine ring were synthesized on the basis of N-furo(thieno, pyrazol, isoxazolo)-N'-methoxycarbonyltrihaloacetamidines [86, 87].

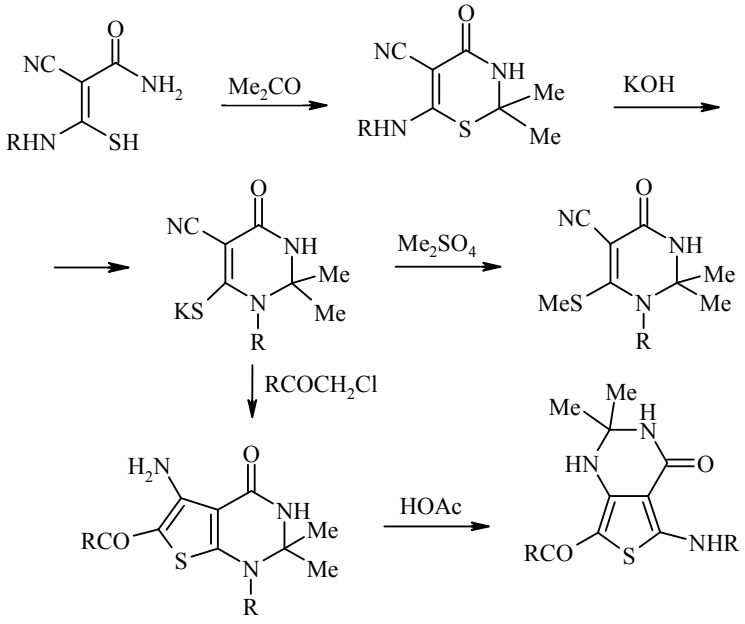
P. S. Lebed and M. V. Vovk first investigated the reaction of 1-chloroalkylheterocumulenes and N-(1-chloroalkylidene)carbamates with a series of derivatives of 2(3)-azaheterylacetic acids [88]. The isomeric trifluoromethyl-containing pyrido[1,2-*c*]pyrimidines and pyrimido[6,1-*b*][1,3]benzothiazoles were obtained by the cyclization of 1-chloroalkyl isocyanates with the esters and nitriles of 2-pyridyl(benzothiazolyl)acetic acids [89]. Cyclocondensation of 1-chloroalkyl isocyanates and 1-chloroalkylcarbodiimides with derivatives of 3-(1,2,4)-triazolylacetic acid gave the isomeric 1- and 3-oxo(arylimino)tetrahydro[1,2,4]triazolo[1,5-*c*]pyrimidines. It was shown that 1,1-dichloroalkyl isocyanates and N-(1-chloroalkylidene)carbamates are suitable electrophilic components of heterocyclizations, leading to heterocondensed pyrimidin-1-ones, while 1-chloroalkylcarbodiimides lead to heterocondensed 1(3)-(N-arylamino)dihydropyrimidines.

An nontrivial cyclization of 1-chloroalkylcarbodiimides with triethylamine, new in the chemistry of heterocumulenes, was discovered. It results in the formation of pyrimido-condensed zwitterionic structures of 4-aryl-6-methyl-4-trifluoromethyl-2-triethylammonio-3,4-dihydroquinazolinides [90].

The cyclocondensation of 1-chloroalkylcarbodiimides with derivatives of azaheterylacetic acids was realized for the first time. It was established that N-(1-aryl-1-chloro-2,2,2-trifluoroethyl)-N'-arylcarbodiimides react with derivatives of 2-pyridyl-, 2-benzothiazolyl-, and 2-benzimidazolylacetic acids to form condensed 1-(N-arylimino)-3-trifluoromethyldihydropyrimidines. The cyclization of 1-chloroalkylcarbodiimides with the nitriles of 3-(1,2,4)-triazolylacetic acid leads to 1-N-arylimino derivatives, while cyclization with the esters of this acid leads to regioisomeric 3-N-arylimino derivatives [89].

Previously unknown cyclizations were discovered during investigation of the chemical transformations of heterocondensed pyrimidines: 2,3-Dihydro-1H-pyrido[1,2-*c*]pyrimidin-3-ones(thiones) to derivatives of 1,3-oxazolidines and 1,3-thiazolidines under the influence of α-bromo ketones and ethyl bromoacetate; heterocondensed 1H-4-cyano-3-trichloromethylpyrimidin-1-ones to 1,2,4-trichloromethyltriazol-3-yl-2-heteryl-ideneacetonitriles by the action of hydrazine hydrate.

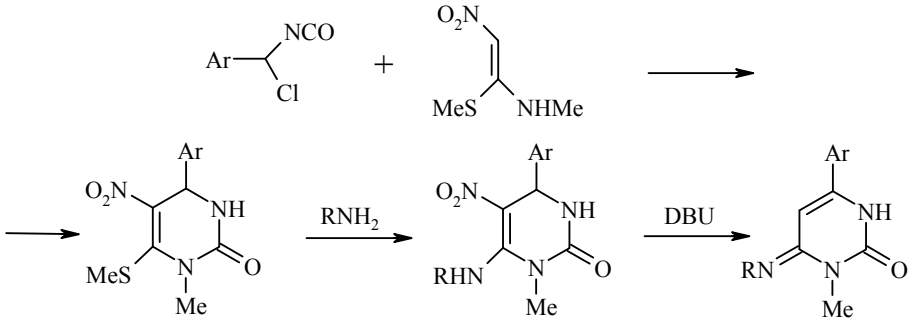
V. A. Sukach, A. V. Bolbut, and M. V. Vovk proposed two procedural approaches to the synthesis of new highly functionalized derivatives of 2,3(3,4)-dihydro-1,3-azin-4(2)-ones and their condensed analogs. The first of them involves the principle of the construction of the 1,3-azine ring by a [5+1] heterocyclization mechanism and is based on the reaction of available 2-alkyl(aryl)amino-1-cyano-2-mercapto-acrylamides with carbonyl compounds [91]. The second is based on a new variant of the formation of the heterocyclic ring by a [3+3] cyclocondensation mechanism, which was realized successfully on examples of the reaction of 1-chloroalkyl isocyanates with 1,3-C,N-, 1,3-C,O-, and 1,3-C,S-binucleophilic reagents [91, 92].



As a result of the experiments the published data concerning the structure of the products from the condensation of 2-alkyl(aryl)amino-1-cyanacryl-2-mercaptoamides with aldehydes and ketones were rejected, and it was established that they are in fact derivatives of 6-alkyl(aryl)amino-2,3-dihydro-1,3-thiazin-4(1H)-one. The possibility of converting these compounds into the thiolates of 6-mercapto-2,3-dihydropyrimidin-4(1H)-one by the action of bases was demonstrated for the first time. The thiolates give S-alkylated products during reaction with dimethyl sulfate and are converted into the original thiazinones during treatment with dilute hydrochloric acid. During alkylation of 2,3-dihydro-1,3-thiazin-4(1H)-ones with α-halo ketones derivatives of 2,3-dihydrothieno[2,3-*d*]pyrimidin-4(1H)-one are formed as a result of recyclization of the thiazine ring and subsequent intramolecular Thorpe condensation. During heating in acetic acid it was found that they are susceptible to transformation into the isomeric heterocyclic system of 2,3-dihydrothieno[3,4-*d*]pyrimidin-4-(1H)-one. The effect of temperature and the nature of the substituents on the course of this process was studied in detail [91, 92].

In order to synthesize difficultly obtainable functionally substituted 2,3-dihydro-1,3-thiazin-4(1H)-ones the reactions of 1-chloroalkyl isocyanates with N,N-cycloalkylaminocyanothioacetamides were investigated. It was shown that in the case of 1-chlorobenzyl isocyanates the corresponding 6-(N,N-cycloalkylamino) derivatives of 2,3-dihydro-1,3-thiazin-4(1H)-one are formed. Depending on their electrophilic characteristics, 1-aryl-1-chloro-2,2,2-trifluoroethyl isocyanates can give both the analogous thiazine heterocycles with a trifluoromethyl group and the products of noncyclic structure – 2-aryl-1-cyano-3,3,3-trifluorothiocrotonamides [93].

It was established that the regioselectivity of the cyclocondensation of 1-chloroalkyl isocyanates with 1,3-diketones and derivatives of 4-hydroxypyran-2-one depends on the structure of the isocyanate component and leads to 3,4-dihydro-1,3-oxazin-2-ones or the structurally isomeric 2,3-dihydro-1,3-oxazin-4-ones. On the basis of the obtained data a scheme was first proposed and realized for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones (Biginelli compounds) based on the cyclocondensation of 1-chlorobenzyl isocyanates with deactivated enamines – the esters of β-aminocrotonic acid and N,S(N,N)-nitroketene acetals. As a result previously difficultly obtainable 1-aryl-substituted derivatives of this important heterocyclic system functionalized at position 6 were obtained. The synthesized 6-methylthio-5-nitro-3,4-dihydropyrimidin-2(1H)-ones are convenient synthesis blocks for reactions with aliphatic and aromatic amines, and this made it possible to obtain a series of various 6-amino derivatives of 3,4-dihydropyrimidin-2(1H)-one, which were denitrosated to derivatives of cytosine when heated in the presence of a strong base [93, 94].



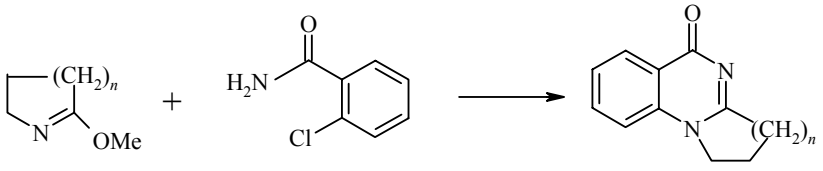
The Use of Lactam Derivatives in the Synthesis of Heterocycles

One of the directions of investigations into the chemistry of heterocyclic compounds pursued at the Institute is the development of methods for the synthesis of azaheterocycles containing a saturated fragment in their structure. Such compounds include condensed heterocyclic systems with one or several saturated rings and

also ω-aminoalkyl-substituted heterocycles. These types of heterocycles have attracted attention in connection with their closeness to natural compounds and also their varied use as pharmaceutical products, pesticides, etc.

There are two main approaches to the production of partly saturated compounds of this type – the reduction of heteroaromatic compounds and the use of saturated functional derivatives in heterocyclizations. A fruitful direction in the synthesis of both polymethylene and ω-aminoalkyl heterocycles is the use of so-called activated forms of lactams – lactim and thiolactim ethers, lactam acetals, imidoyl chlorides, etc. – as intermediates. The high reactivity and the availability of these compounds make it possible to use them widely in heterocyclizations or to obtain the corresponding cyclic amidines and enamines, which are also valuable starting compounds in the synthesis of various azaheterocycles.

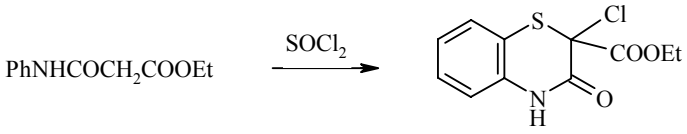
An example of the successful use of this approach is the method of synthesis of benzannelated 1,2-polymethylene derivatives of 1,3-diazaheterocycles. The method involves cyclization of N-(2-haloaryl)amidines and their N-acyl and N-sulfonyl derivatives as a result of intramolecular arylation. The initial compounds can be obtained in one stage from lactim ethers or cyclic imidoyl chlorides and 2-haloanilines, 2-halobenzamides, or 2-halobenzenesulfonamides. Two methods were developed for their cyclization to polymethylene derivatives of benzimidazole, 4-quinazolone, and 1,2,4-benzothiadiazine 1,1-dioxide depending on the nature of the halogen, the size of the saturated ring, and the presence of electron-withdrawing substituents in the aromatic ring. One of them is thermal cyclization, involving the heating of the initial compounds above 150°C. The method is suitable for the synthesis of 1,2-polymethylenebenzimidazoles with accepting substituents (K. G. Nazarenko, T. I. Shirokaya) [95], and also derivatives of 1,2-polymethylene-4-quinazolone [96].



Another method involves the use of the CuI–ligand system as catalyst of intramolecular arylation. Such an approach gives excellent results for the bromine derivatives of amidines and sulfonylamidines. In this case the cyclization is realized under mild conditions (80°C, acetonitrile), while the yields of the final products depend little on the size of the saturated ring and the presence of accepting substituents in the aromatic ring. By combining these two methods it is possible to obtain a wide range of derivatives of 1,2-polymethylene-1,3-diazaheterocycles with various substituents both in the aromatic ring and in the saturated bridge. Thus, the investigations made these derivatives of benzimidazole, and 4-quinazolone, readily available and opened up wide possibilities both for the search for biologically active compounds among them and for their further use in the synthesis of more complex heterocyclic systems [97].

Recyclization reactions involving lactim and thiolactim ethers and also the cyclic amidines and enamines obtained from them were studied [98].

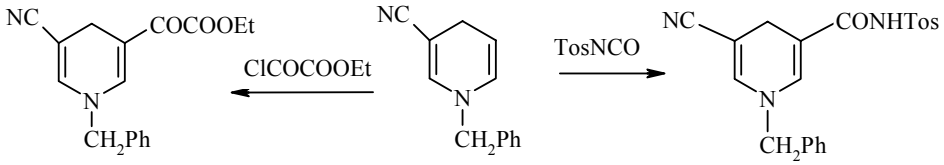
2-Chloro-2-ethoxycarbonyl-4H-benzo[1,4]thiazine-3-ones [99], from which various 2-aryl and 2-heteryl derivatives are easily obtained, were synthesized [100-102].



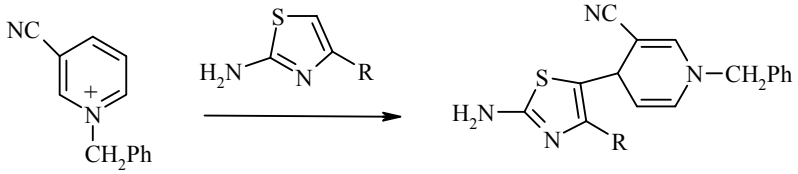
Production of Dihydropyridines

A. N. Kostyuk and D. M. Volochnyuk made a substantial contribution to methods for the functionalization of dihydropyridines. They showed that 5-unsubstituted 1,4-dihydropyridines that have

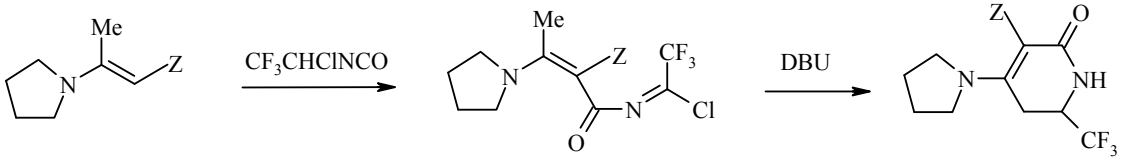
electron-withdrawing groups at position 3 are suitable for electrophilic functionalization. N-Benzyl-3-cyano-1,4-dihydropyridine is acylated selectively by such highly active reagents as ethyloxalyl chloride and tosyl isocyanate with the formation of the corresponding derivatives. Its phosphorylation gives the possibility of obtaining a series of phosphorylated derivatives [103].



It was found that 5-aminopyrazoles, 5-aminoisoxazole, 2-aminothiazoles, and 6-aminouracils add with high yields to N-benzyl-3-cyanopyridinium chloride with the formation of the corresponding N-benzyl-3-cyano-4-hetaryl-1,4-dihydropyridines [104].



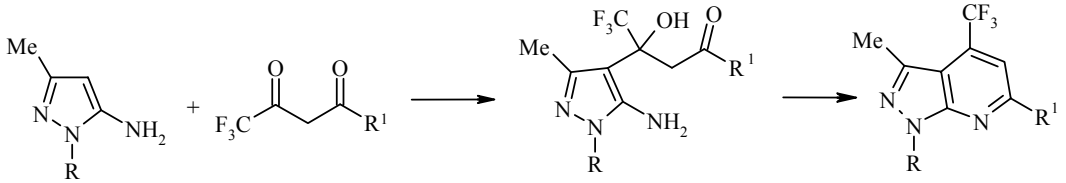
A. N. Kostyuk, D. M. Volochnyuk, and D. A. Sibgatulin showed that α-chloro-β,β,β-trifluoroethyl isocyanates react with α-methyl-substituted enamines in the presence of triethylamine at the β-position of the enamine with the formation of carbamoyl derivatives of acylamines that in the presence of moisture form enamides, which cyclize to derivatives of 5,6-dihydropyridin-2-ones during the action of strong bases DBU or DBN [105].



Z = CN, COOEt, COMe, COPh

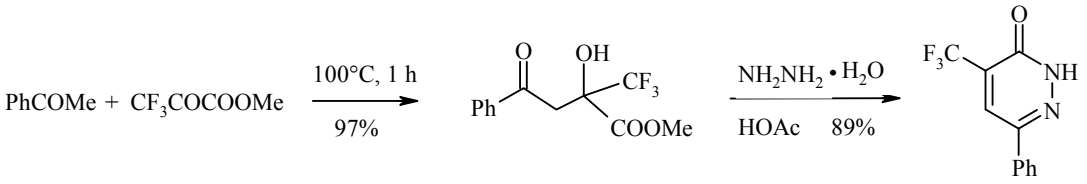
Synthesis of Fluoroalkyl-substituted N-Containing Heterocycles

D. M. Volochnyuk, D. A. Sibgatulin, *et al*. developed a convenient method for the synthesis of trifluoromethyl-substituted condensed heterocycles involving the reaction of trifluoro-substituted 1,3-diketones with a series of electron-rich amino heterocycles. The reaction takes place regioselectively with high yields [106].

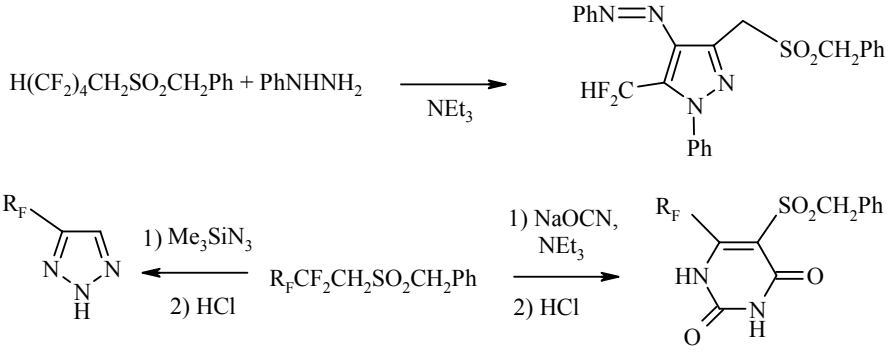


R = Me, Ph

A. N. Kostyuk, D M. Volochnyuk, and D. A. Sibgatulin developed a new approach to the synthesis of 4-trifluoromethylpyridazin-3-ones based on the reaction of enamines with methyl trifluoropyruvate followed by cyclization of the obtained products with hydrazine [107].



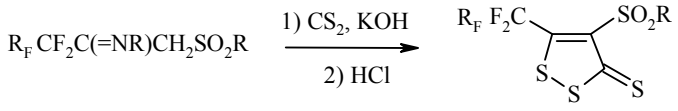
1,1-Dihydropolyfluoroalkyl sulfones have been widely used for the synthesis of various polyfluoroalkyl-substituted nitrogen-containing heterocycles (pyrroles, pyrazoles, triazoles, uracils, pyrimidines) (V. M. Timoshenko, Yu. G. Shermolovich) [108-110], for example:



Chemistry of Sulfur-Containing Heterocycles

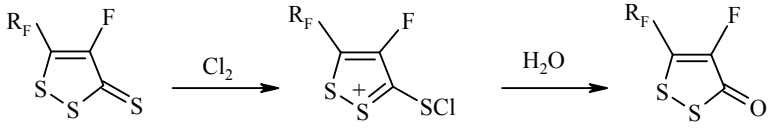
Polyfluoroalkanedithiocarboxylates in cycloaddition reactions with dimethyl acetylenedicarboxylate give derivatives of 1,3-dithioles [111].

In the reaction of β-polyfluoroalkyl-β-iminosulfones with carbon disulfide in an alkaline medium followed by acidification with hydrochloric acid a mixture of substituted 1,2-dithiole-3-thiones is formed.

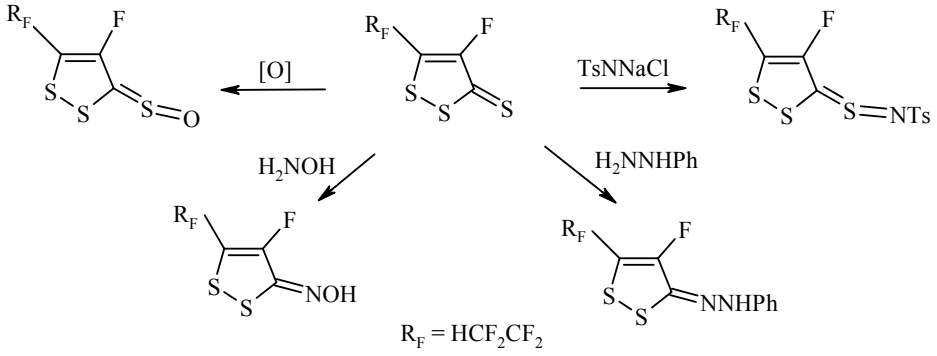


4-Fluoro-5-polyfluoroalkyl-3H-1,2-dithiole-3-thiones are formed when α,β-unsaturated β-bromodithioesters are heated with elemental sulfur [112].

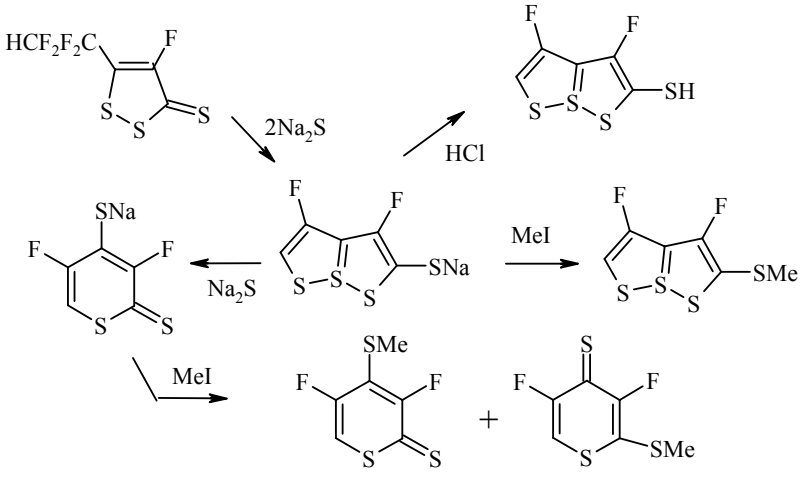
Dithiolethiones are chlorinated under mild conditions with the formation of 3-chlorothio-1,2-dithiolium salts, which are readily hydrolyzed with the formation of 1,2-dithiol-3-ones, while the reaction with alkyl- or arylamines gives the products from substitution of the exocyclic sulfur atom by an imino group – 3-imino-1,2-dithiolenes.



Dithiolethiones are readily oxidized by *meta*-chloroperbenzoic acid to sulfines and are also oxidized by chloroamines to sulfinimides [113, 114]. Dithiolethiones condense with hydroxylamine and hydrazines to form oximes and hydrazones.



In the reaction of dithiolethione with two equivalents of sodium sulfide followed by acidification of the reaction mixture a 2-mercapto derivative of trithiapentalene is formed, and after addition of methyl iodide to the reaction mixture the 2-methylthio derivative is formed. In the reaction of dithiolthione with three equivalents of sodium sulfide 4-mercaptothiopyran-2-thione is formed after acidification. Treatment of the reaction mixture with methyl iodide leads to the formation of a mixture (1:1) of two isomeric thiopyranthiones (I. I. Fesun, V. M. Timoshenko, A. B. Rozhenko) [115].

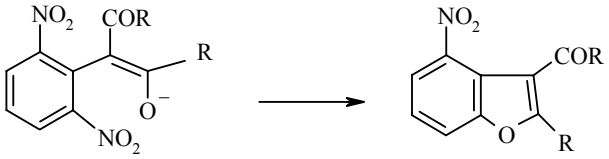


Thus, methods have been developed for the synthesis of fluoropolyfluoroalkyl-substituted 1,2-dithiole-3-thiones, which are convenient starting materials for the synthesis of new fluorine-containing heterocycles with a sulfur atom (dithiol-3-ones and imines, oximes, hydrazones, ylidenes, sulfinimides, and sulfines, halo-substituted dithiolanes). It was shown that the reaction of 5-tetrafluoroethyl-4-fluoro-1,2-dithiole-3-thione with sodium sulfide leads to fluorine-containing derivatives of thiopyranthione or trithiapentalene (V. M. Timoshenko, Yu. G. Shermolovich) [114, 115].

Heterocyclization Based on Aromatic Polynitro Compounds

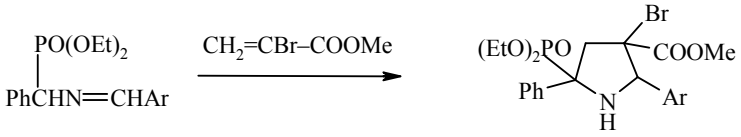
The search for ways of transforming polynitro aromatic compounds is important in the light of their availability. It was shown that β-dicarbonyl derivatives of dinitro- and trinitrobenzenes are easily converted into functionalized benzofurans by intramolecular substitution of the nitro group [116].

The transformations of di- or trinitrotoluenes into the corresponding aldehydes and subsequent reaction with arylamines lead to intramolecular heterocyclization with the formation of functionalized indazole 1-oxides [117].



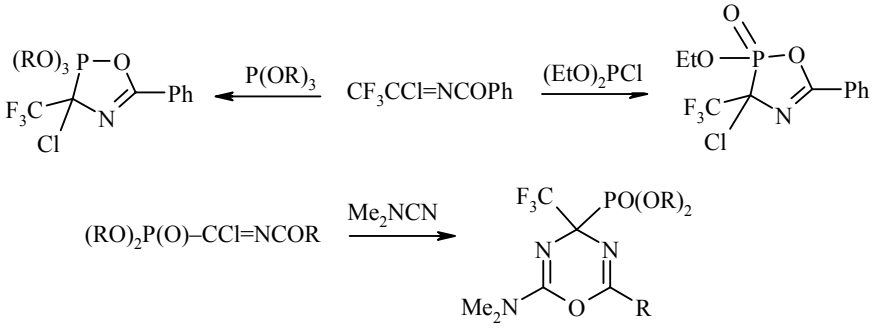
Nitrogen-Containing Heterocycles Based on Phosphorylated Imines and Functionalized Heterodienes

Methods were developed for the synthesis of nitrogen-containing heterocycles on the basis of phosphorylated azaallylic systems. For the construction of heterocycles it is possible to use an azaallyl fragment, an azomethine bond, or a 1,3-heterodiene system. The presence of an activating phosphorus group in arylideneaminophosphonates gives rise to the possibility of a 1,2H-shift and the generation of azomethine ylides, which readily form mono- and bicyclic derivatives of phosphorylated pyrrolidines during reaction with dipolarophiles [118-120].



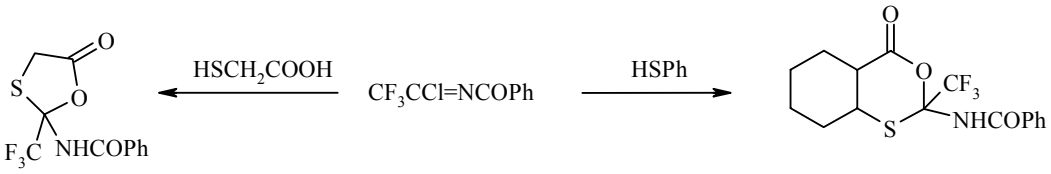
The stereoselectivity of cycloaddition depends on the method of generation of the azomethine ylides. The simultaneous presence of activating (COOR) and nucleofugic (Br) substituents in the dipolarophile makes it possible to obtain condensed three- and four-membered nitrogen-containing heterocycles with fragments of aminophosphonic and aminocarboxylic acids [119, 120].

The cyclization of imines with α-mercaptocarboxylic acids at the C=N bond opens up the way to derivatives of thiazolidones with a phosphoryl group [121-124]. Syntheses of the functionalized heterodienes used in the production of five- and six-membered heterocycles as a result of [4+1] and [4+2] cycloaddition reactions were realized. By such a method it is possible to obtain oxazaphospholines [125-133], phosphorylated oxadiazines [134], dihydrooxazines and dihydrooxazoles [133-135], for example:



The high reactivity of activated iminocarboxylates makes it possible to use these systems for the aminoalkylation of electron-rich heterocycles. Functionalized indoles containing fragments of trifluoroalanine, in particular, were synthesized by this method [136].

A simple method based on imidoyl chlorides and mercaptocarboxylic acids was developed for the synthesis of biologically promising 1,3-oxathiolan-5-ones and 3,1-benzoxathian-4-ones containing a protected amino group and a polyfluoroalkyl substituent at the C(2) atom of the heterocycle. A special feature of the new heterocyclization is the fact that the imine carbon atom acts as a 1,1-electrophile while the carboxyl function reacts with its own O-nucleophilic center [137].

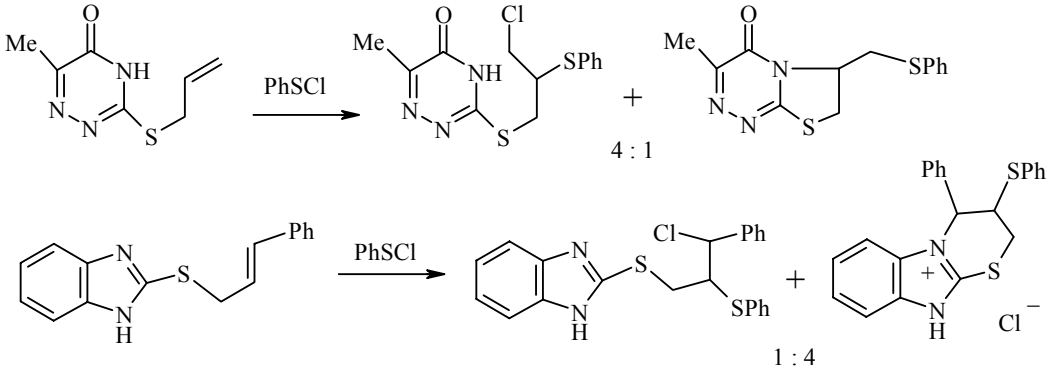


It was shown that the reaction of the sulfonylimines of trifluoropyruvate with phosphites leads to oxazaphospholines with a pentacoordinated phosphorus atom, which rearrange spontaneously with transfer of the sulfonyl group from the nitrogen to the carbon and the formation of C-sulfonyl derivatives of trifluoroalanine [132].

Syntheses of Heterocyclic Compounds by Electrophilic Intramolecular Cyclization Reactions of Olefins and Acetylenes

As a result of investigations it was established that the reactions of derivatives of 2-allyl-, 2-cinnamyl-, and 2-propargylthienopyrimidine, which take place with the participation of electrophiles, can be directed toward the formation of angular (by the action of iodine, bromine, selenium dioxide, and haloid acids) or linear (by the action of concentrated sulfuric acid) derivatives of thiazolino-, trihydrothiazino-, thiazolo-, and dihydroselenothiazinothienopyrimidine [138].

Relationships were established for the arylsulfenylchlorination of a series of S-alkenyl- and S-alkynyl-substituted di-, tri-, and tetranitrogen-containing heterocycles. In a nonpolar solvent the reactions take place predominantly with the formation of products from electrophilic addition against the Markovnikov rule. In a polar solvent the products from intramolecular cyclization according to the Markovnikov rule are mostly formed and with quantitative yields if additions of lithium perchlorate are made to the reaction mixture (V. I. Staninets, A. I. Vas'kevich, R. I. Vas'kevich) [139-143], for example:



The nucleophilic substitution of the halogens in the products from bromo- and iodocyclization of 2-(2-propenylthio)-4(1H)-quinazolinone by the action of amines or the potassium salts of heteroaromatic thiols was studied. As a result functionally substituted derivatives of thiazoloquinazolinone were obtained. Antioxidant characteristics were discovered, and the ability of the synthesized compounds to exhibit cardioprotective and vasodilatory activity was demonstrated [144-146].

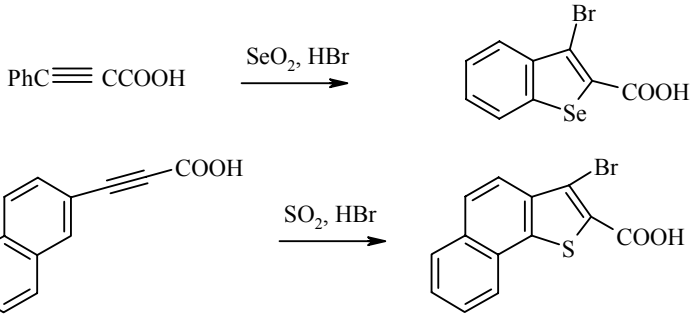
Electrophilic addition to unsaturated compounds was widely used for the synthesis of various heterocyclic systems, but selenium- and tellurium-containing electrophiles had previously been studied insufficiently in such reactions.

It was shown that the reaction of derivatives of 2-propargylthio-5-R-1,3,4-oxadiazoles with phenylselenium trihalides leads to the formation of 6-halomethylene-2-R-1,3,4-oxadiazolo[3,2-*b*][1,4,2]thiaselenazinium halides, while the reaction of 2-allylthio-5-R-1,3,4-oxadiazoles with phenylselenium trihalides gives 1:1 adducts [147, 148].

New variants of electrophilic intramolecular cyclization were discovered, for example, in the tandem heterocyclization of di(3-allyl-4-oxothieno[2,3-*d*]pyrimidin-2-yl) disulfides, the heterocyclization of hetarylthiosemicarbazides by the action of alkyl halides, and of 2-alkenyl-substituted ureas and thioureas by the action of thionyl chloride [145, 149, 150].

A method was developed for the heterocyclization of olefins and acetylenes by the action of selenium and tellurium tetrahalides under phase-transfer conditions (water–diethyl ether), which made it possible to increase the yields of the heterocyclic compounds [148, 151, 152].

A new reaction was discovered for the oxidation–reduction heterocyclization of acetylenes by the action of chalcogen dioxides and hydrogen halides, during which sulfur- and selenium-containing heterocyclic compounds are formed [138, 153-155], for example:



New Reagents for Heterocyclization

Derivatives of phthalazin-1(2H)-one, pyrido[2,3-*d*]pyridazin-5(6H)-one, furo[2,3-*d*]pyridazin-4(5H)-one, and 8-R-3,4-dihydro-4H-pyridazino[4,5-*b*]indol-4-ones were obtained as a result of the heterocyclization of *o*-aldehydoacids (esters) of the carbo- and heterocyclic series with bifunctional reagents. The heterocyclization of 5-R-2-ethoxycarbonyl-3-formylindoles with enaminones of the heterocyclic series were studied for the case of 6-aminouracils. 1-Hetaryl-3-oxo-1,3-dihydro-2-isobenzofurans were synthesized by the reaction of *o*-aldehydoacids of the aromatic series with substituted derivatives of indole and 5-aminopyrazole [156].

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