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REACTIONS OF 1,4-*NCCN*-, 1,4-*NNCN*- AND 1,5-*NCCCN*-BINUCLEOPHILES WITH DICARBOXYLIC ACIDS CYCLIC ANHYDRIDES AS A METHOD OF HETEROCYCLIC COMPOUNDS SYNTHESIS (A REVIEW)

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Critical analysis of published information related to the features of reaction of 1,4-NCCN-, 1,4-NNCN and 1,5-NCCCN-binucleophiles with cyclic anhydrides of dicarboxylic acids has been presented in the review. It has been shown that the reaction of named anhydrides with 1,4-NCCN-binucleophiles leads to the formation of the imidazole fragment that contains carboxyl-containing moiety. It has been shown that benzimidazole derivatives are among the most studied products of reaction between 1,4-NCCN- and cyclic anhydrides of dicarboxylic acids due to the high availability of initial compounds. The approaches to chemical modification of latter compounds have been discussed as well. It has been found out that 1,4-NNCN-binucleophiles used in reactions with cyclic anhydrides of dicarboxylic acids are mostly presented by amidines and amidrazones. The effects of structures of initial compounds and conditions of reactions on the products of reaction have been described. Literature data shows that the reaction of 1,5-NCCCN-binucleophiles such as amides and hydrazides of anthranilic acid, diamino-substituted polycyclic arenes and 2-azaheterylanilines with cyclic anhydrides of dicarboxylic acids commonly results in the formation of pyrimidine derivatives. It has been established that the application of cyclic anhydrides of non-symmetric dicarboxylic acid as reagents may cause the ambiguity of the reaction pathways. However, the formation of single products of interaction between binucleophiles and non-symmetric anhydrides can be achieved by variation of reaction conditions. The biological activity of the discussed reaction products has been considered in detail. It has been shown that the above-mentioned compounds reveal antibacterial, antifungal, anticancer, immunomodulate, and antidiabetic activities.

Keywords: binucleophile, cyclic anhydride of dicarboxylic acid, amine, hydrazine, 2-azaheterylaniline, heterocycle, biological activity.

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Introduction

Heterocyclic compounds are among the most interesting objects for studies aimed to the elaboration of novel medications [1–3]. Numerous approaches for synthesis of heterocyclic substances were elaborated considering their roles in various branches of industry. 1,4-NCCN-, 1,4-NNCN and 1,5-NCCCN-binucleophiles are considered to be one of the most valued initial compounds for preparation of heterocycles, which can be explained by their synthetic availability and wide possibilities of chemical modification. One of the most promising directions for synthesis of biologically active heterocycles is the reaction of abovementioned binucleophiles with cyclic anhydrides of dicarboxylic acids. Thus, above-mentioned reaction allows the preparation of heterocyclic compounds that contain pharmacophoric carboxylic groups in their structure. It should be noted that despite the prospects of this reaction the reviews that devoted to it has not been published. Considering the mentioned fact, it was decided to generalize the available information about

the features of reaction between 1,4-NCCN-, 1,4-NNCN and 1,5-NCCCN-binucleophiles and cyclic anhydrides of dicarboxylic acids, as well as biological properties of products of this reaction.

Reaction of 1,4-NCCN-, 1,4-NNCN-binucleophiles with cyclic anhydrides of dicarboxylic acids as method of heterocyclic compounds synthesis

o-Phenylenediamine and its derivatives in reactions with cyclic anhydrides of dicarboxylic acids

Among first papers dedicated to this issue should be considered publications by Fisher and co-authors [4,5]. In particular, they cover the reactions of 4-methyl-N^1-p-tolylbenzene-2-diamine (1.1) with succinic and phthalic anhydrides (Fig. 1).

These authors also studied the reactivity of abovementioned anhydrides towards N^2-phenylnaphthalene-1,2-diamine (1.4) (Fig. 2). It should be noted that the proposed structures 1.3 and 1.6 are controversial, since the use of phthalic anhydride in such reactions can lead to the formation of the corresponding phthalimides, which are isomeric to proposed products with a free carboxylic group. Moreover, it is impossible to establish the structure of reaction products by the methods used by the authors.

Meyer and Maier [6] studied the interaction of o-phenylenediamine (1.7) with succinic anhydride in ethanol at the temperature of 150−180^{0}C (Fig. 3). The researchers found that the main product of the reaction is a compound 1.8, while the compounds 1.9 and 1.10 are minor products. In addition, resynthesis 1.8 is given in the work [7] and its functional derivatives (esters, amides, salts) were obtained.

Chatterjee [8] has optimized the method of the compound 1.8 preparation via interaction of compound 1.7 with two equivalents of succinic anhydride when heated in xylene. The synthesis of functional derivatives 1.11 and 1.12 is described in the work as well (Fig. 4).

Modification of compound 1.8 by introduction of the ethoxy fragment to 5th position of the aromatic system leads to the formation of a substance 1.15. Subsequential esterification (1.16) and synthesis of amide (1.17) were conducted as well (Fig. 5).

Lieb [9] described the interaction of naphthalene-1,2-diamine (1.18) with phthalic anhydride (Fig. 6). According to the author, the reaction product is 2-(1H-naphth[1,2-d]imidazol-2-yl)benzoic acid (1.19). The cyclization of compound 1.19 resulted in the formation of product 1.20.

A new approach to the synthesis of 3-(1H-benzimidazol-2-yl)propanoic acids is presented in

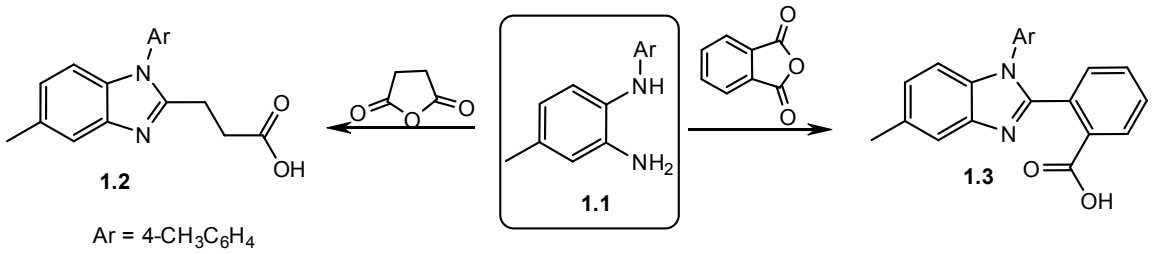

Fig. 1. The reaction of 4-methyl-N^1-p-tolylbenzene-2-diamine with succinic and phthalic anhydrides

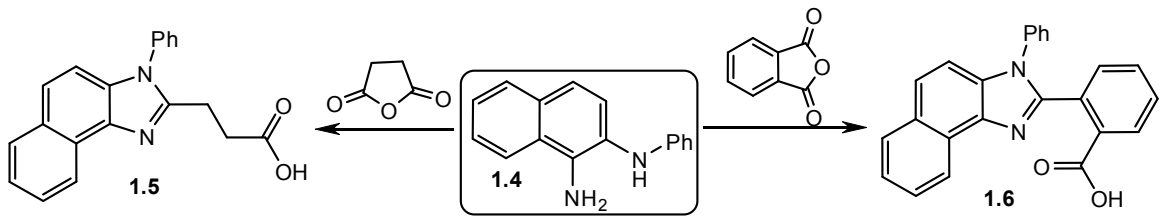

Fig. 2. The reaction between N^2-phenylnaphthalene-1,2-diamine and anhydride of succinic and phthalic acids

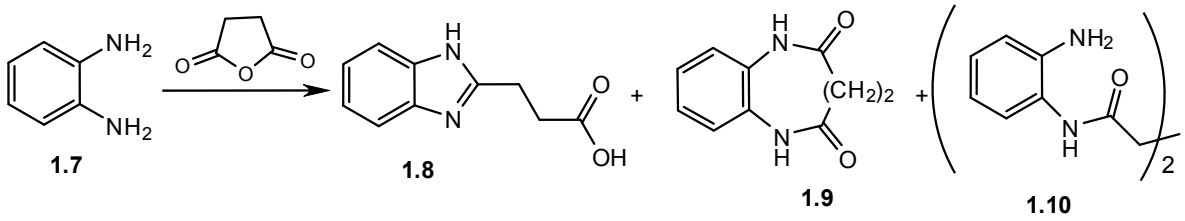

Fig. 3. Features of the reaction of o-phenylenediamine with succinic anhydride

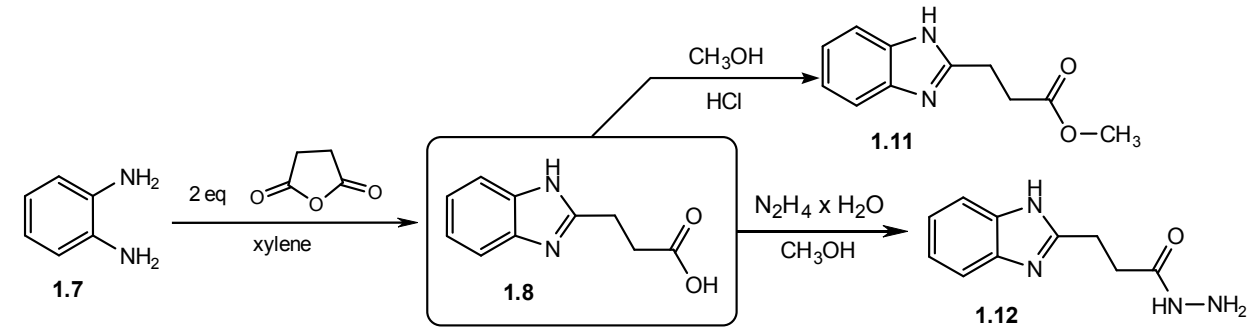

Fig. 4. The optimized synthetic approach for 3-(1H-benzimidazol-2-yl)propionic acid

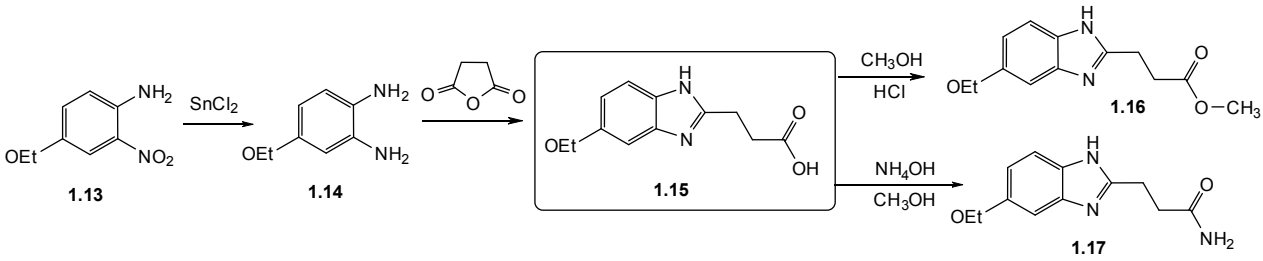

Fig. 5. Synthesis of 3-(5-ethoxy-1H-benzimidazol-2-yl)propanoic acid and its functional derivatives

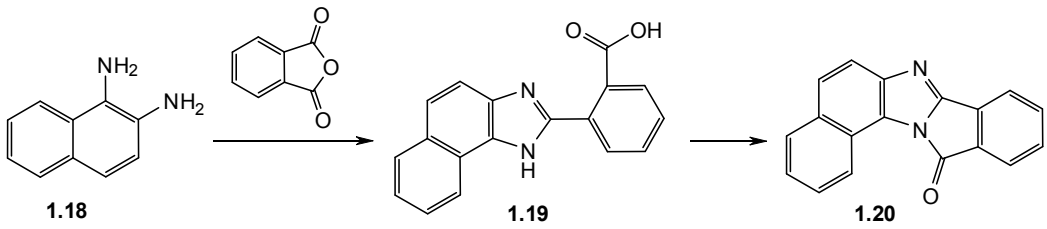

Fig. 6. Cyclocondensation based on naphthalene-1,2-diamine and phthalic anhydride

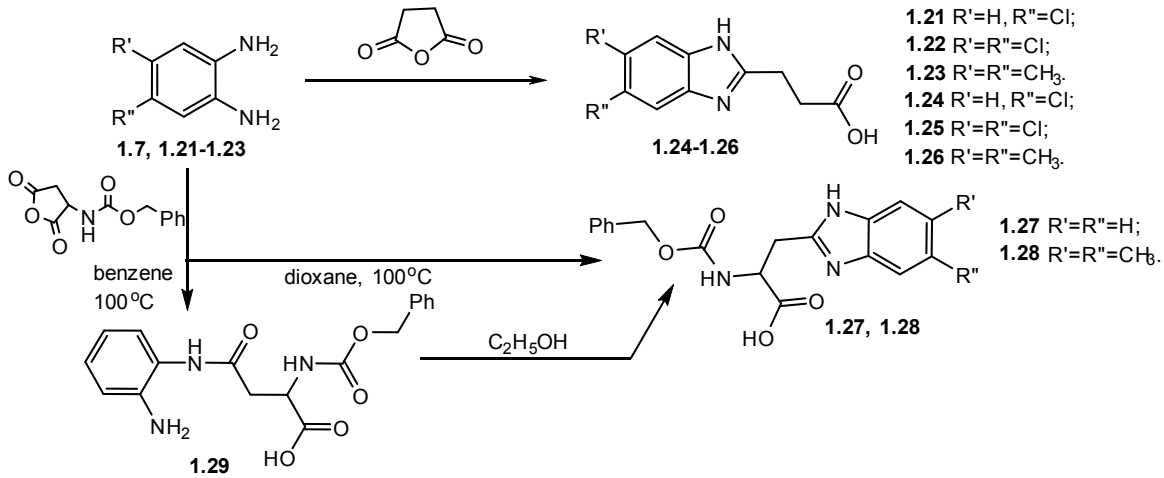

Fig. 7. Cyclocondensation of substituted o-phenylenediamine with succinic anhydride and its derivatives

the paper [10]. Thus, 5,6-disubstituted derivatives 1.24-1.26 have been synthesized (Fig. 7). Reactions of o-phenylenediamine (1.7) and 4,5-dimethyl-derivative (1.23) with substituted succinic anhydride have been studied for the first time as well (Fig. 7). The authors state that, depending on the reaction conditions (dioxane or benzene), the formation of both corresponding N-[(benzyloxy)carbonyl]-3-(5,6-dimethyl-1H-benzimidazol-2-yl)alanines (1.27, 1.28) and amide 1.29 is possible. It is important that the

latter undergoes cyclocondensation under refluxing in absolute ethanol with the formation of 1.27. It is also noted in the work that the corresponding methyl esters and amides are obtained for the compounds 1.24-1.26.

Hein et al. [11] refers elaborated methods for the synthesis of benzimidazole, benzoxazole and benzothiazole derivatives using [4+1]-cyclocondensation reactions in which the cyclizing agent is polyphosphoric acid. In particular, the reaction of o-phenylenediamine (1.7) and phthalic anhydride (Fig. 8) was investigated. Additionally, authors estimated the absorption maxima in the UV-part of the compound 1.30 spectrum (λ_{max}=297 nm, e=$1.31 \cdot 10^{-4}$). However, UV spectroscopy is not a valid method for evaluation of the obtained compounds structure, therefore the probability of formation of isomeric phthalimide was not excluded.

The use of succinic anhydride for the formation of heterocyclic systems is shown in the article [12]. Thus, the reaction of 3,6-dimethoxy-o-phenylenediamine (1.31) with above-mentioned anhydride resulted in the formation of 3-(4,7-dimethoxy-1H-benzimidazol-2-yl)propanoic acid (1.32), which was isolated as hydrochloride (1.33) with the yield of 40% (Fig. 9).

Yang [13] studied the peculiarities of the reaction of o-phenylenediamine (1.7) with substituted succinic anhydride in solvents with different dielectric constant (dioxane, THF, DMF, N,N-dimethyl-acetamide, and DMSO) (Fig. 10).

The conclusions on the influence of the solvent on the prevailing direction of the acylation stage 1.7 were made based on the ratio of cyclization products 1.36 and 1.37. Compounds 1.36 and 1.37 underwent cyclocondensation in acetic anhydride to form corresponding products 1.38 and 1.39. The author determined that the increase in the polarity of the solvent led to the formation of compound 1.37 as a major product of reaction, while the usage of nonpolar solvents increased the yield of 1.36. In the study [13] the hypothetical mechanism of the reaction, and the IR- and ^{1}H NMR-spectra of the synthesized compounds were discussed as well. It should be noted that the given data on the formation of two products is not consistent with the work [10].

The reaction of [4+1]-cyclocondensation of 4-[(1H-imidazol-1-yl)methyl]benzene-1,2-diamine

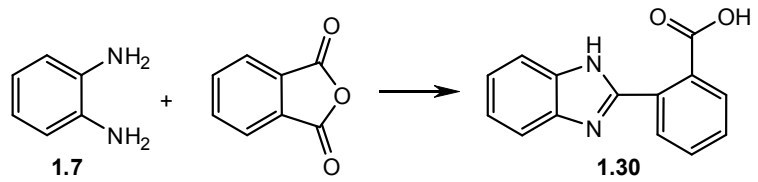

Fig. 8. Cyclocondensation based on o-phenylenediamine and phthalic anhydride

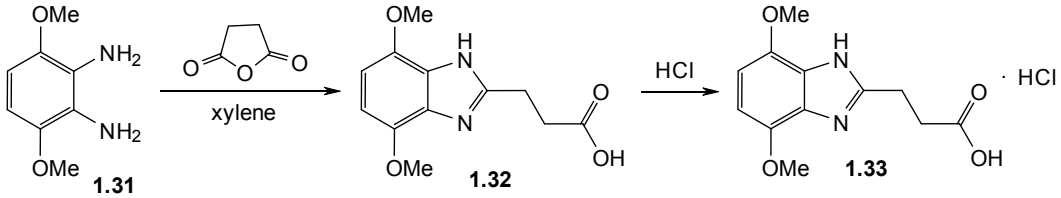

Fig. 9. The synthesis of 3-(4,7-dimethoxy-1H-benzimidazol-2-yl)propanoic acid and its hydrochloride

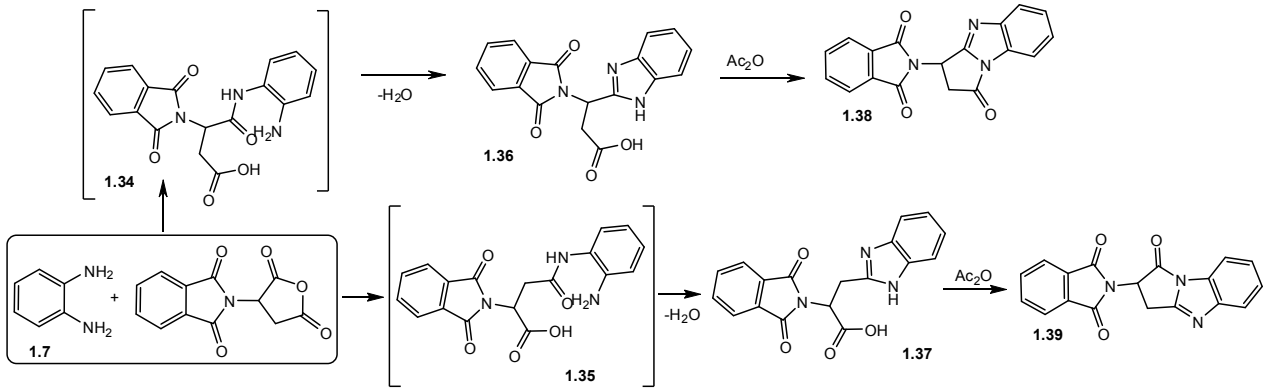

Fig. 10. The features of the reaction of o-phenylenediamine with 2-(2,5-dioxotetrahydrofuran-3-yl)-1H-isoindole-1,3(2H)-dione

(1.40) and phthalic anhydride in a medium of hydrochloric acid was studied [14]. The attempt was not completely successful, since 2-{5-[(1H-imidazol-1-yl)methyl]-1H-benzo[d]imidazol-2-yl}benzoic acid dihydrochloride dihydrate (1.40) was isolated with low yield (10.5%) (Fig. 11).

Salakhov et al. [15] studied the interaction between o-phenylenediamine (1.7) and cis-/trans-forms of cyclohex-4-ene-1,2-dicarboxylic acid anhydride (Fig. 12).

The authors have shown that the interaction of the starting substances in acetone leads to the formation of the corresponding cis- and trans-6-(2-aminophenylcarbamoyl)cyclohex-3-enecarboxylic acids (1.42 and 1.43). The cyclization of the latter in o-xylene or petroleum ether during heating leads to the formation of cis-N-(o-aminophenyl)-4-cyclohexene-1,2-dicarboxamide (1.44). At the same time, the heating of 1.42 and 1.43 in benzene in the presence of an H^+-form cation-exchanger leads to the formation of cis-N-(o-aminophenyl)-4-cyclohexene-1,2-dicarboxamide (1.44) and 6-(1H-benzo[d]imidazol-2-yl)cyclohex-3-enecarboxylic acid (1.45). It should be noted that the authors did not specify the isomeric nature of the product. The given data on the formation of two products are somewhat not consistent with the work mentioned above [10]. This work is noteworthy since the influence of spatial factors and conditions of reactions on the course of appropriate transformations was investigated.

In order to create a combinatorial library of derivatives of 3-(4,5-dioxo-5,6-dihydro-4H-imidazo[1,5,4-de]quinoxalin-2-yl)propanoic acid (1.48), Varano et al. [16] used 3-(4-nitro-1H-benzo[d]imidazol-2-yl)propanoic acid (1.47) as initial substance. The synthesis of the latter one was carried out on the basis of the reaction [4+1]-cyclocondensation between succinic anhydride and 3-nitrophenylene-1,2-diamine (1.46) in the o-xylene medium (Fig. 13).

In all previous publications, classical liquid-phase synthetic methods were used for the reaction [4+1]-cyclocondensation with the use of cyclic anhydrides of dicarboxylic acids. Lingaiah-Boddupally et al. [17] first investigated the interaction of cyclic anhydrides with 1,4-binucleophiles in terms of microwave irradiation in the solid phase. Thus,

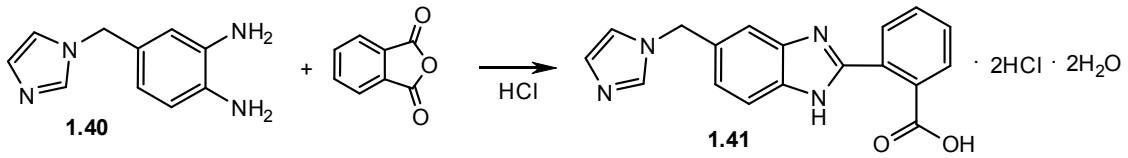

Fig. 11. [4+1]-cyclocondensation of 4-[(1H-imidazol-1-yl)methyl]benzene-1,2-diamine and phthalic anhydride in hydrochloric acid

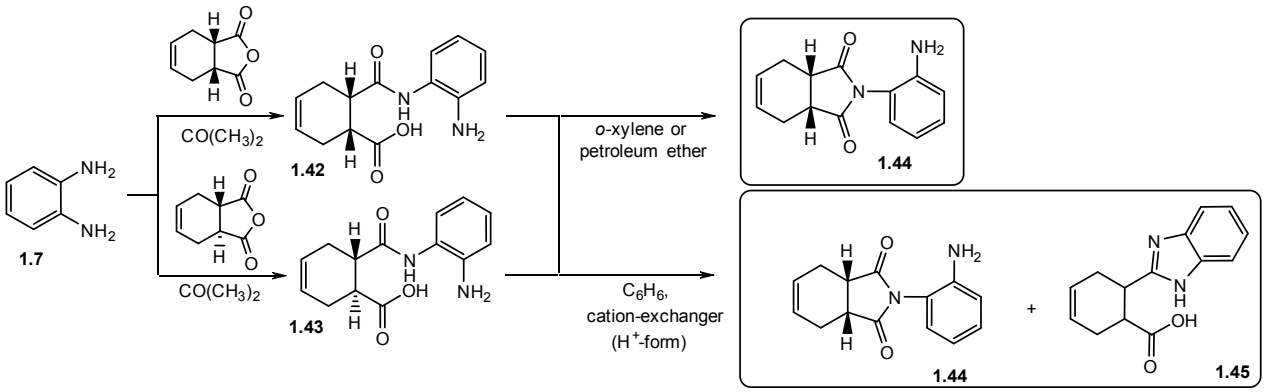

Fig. 12. The interaction of o-phenylenediamine with cis- and trans-forms of cyclohex-4-ene-1,2-dicarboxylic acid anhydride

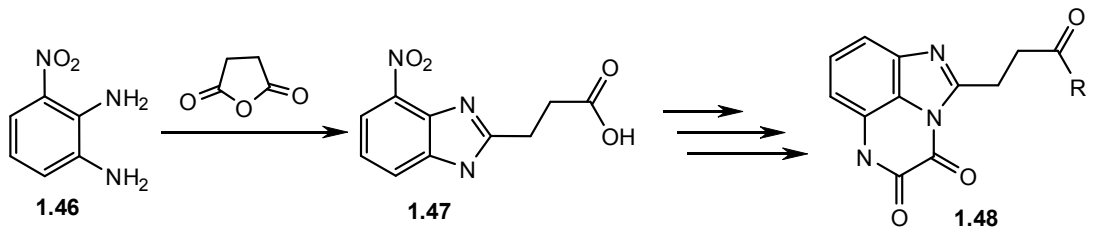

Fig. 13. The synthesis of 3-(4,5-dioxo-5,6-dihydro-4H-imidazo[1,5,4-de]isoquinolin-2-yl)propanoic acid and its derivatives

the interactions of 3-nitro-5-(trifluoromethyl)-benzene-1,2-diamine (1.49) with anhydrides of succinic, maleic, methylmaleic, substituted phthalic and naphthalene-1,8-dicarboxylic acids were investigated (Fig. 14) under irradiation at 450 W on silica gel in the presence of anhydrous zinc chloride forms carboxylic acids (1.51, 1.52, and 1.54–1.56). In the case of the use of 800 W radiation under similar conditions, the products of interaction 1.49 with phthalic and naphthalene-1,8-dicarboxylic acid anhydrides are new heterocyclic systems: isoindolo[2,1-a]benzimidazole (1.53) and benzo[d,e]benzo[4,5]imidazo[2,1-a]isoquinoline (1.52) respectively.

Compounds 1.52 and 1.53 are obtained by alternative method from the corresponding 1.50 and 1.51, respectively, under similar conditions. The structure of the all obtained compounds is proved by spectral analysis methods (IR-, ^{1}H NMR-spectroscopies, and mass-spectrometry) and does not cause any doubts.

A method for the preparation of 2-(1H-benzo[d]imidazol-2-yl)nicotinic acid (1.57) has been developed, which is realized by the interaction of o-phenylenediamine (1.7) with nicotine-2,3-dicarboxylic anhydride in DMF during heating for 3 hours [18] (Fig. 15). According to the authors, the reaction [4+1]-cyclocondensation is realized in this case through the intermediate stage, namely the formation of the corresponding amide.

Sun et al. [19] developed a single-reactor method for the synthesis of methyl 3-(1-(4-methoxyphenyl)-1H-benzo[d]imidazol-2-yl)propionate (1.59) (Fig. 16). The authors managed to find the conditions under which, along with the reaction [4+1]-cyclocondensation, the esterification of the carboxyl group formed during the reaction.

Within the framework of the studies [20,21], the synthesis of the 4-(1H-benzimidazol-2-yl)-3-arylbutanic acid (1.61) is realized by the reaction of substituted o-phenylenediamines (1.60) with a number of anhydrides, derivatives of 3-R-glutaric acid (Fig. 17). To confirm the structure of the compounds, ^{1}H-, ^{13}C-NMR- and mass-spectroscopic

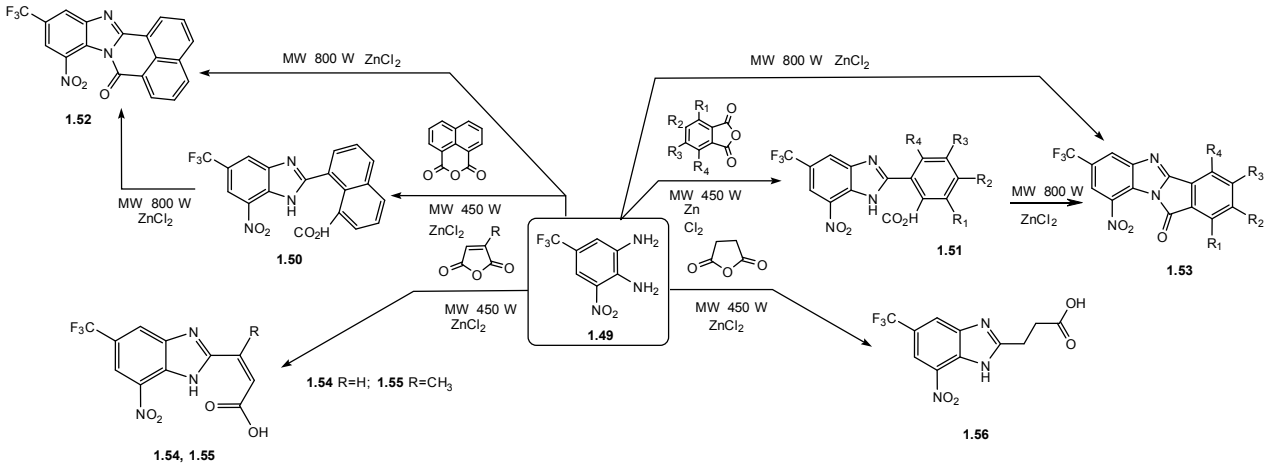

Fig. 14. Interaction of 3-nitro-5-(trifluoromethyl)benzene-1,2-diamine with anhydride of dicarboxylic acids under microwave irradiation

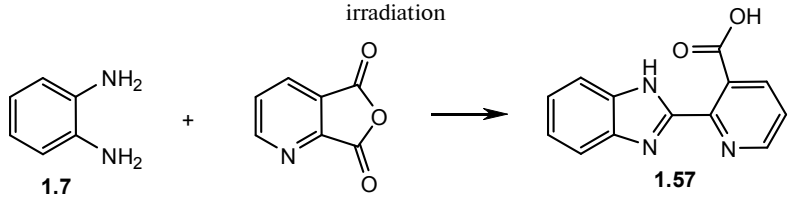

Fig. 15. The synthesis of 2-(1H-benzo[d]imidazol-2-yl)nicotinic acid

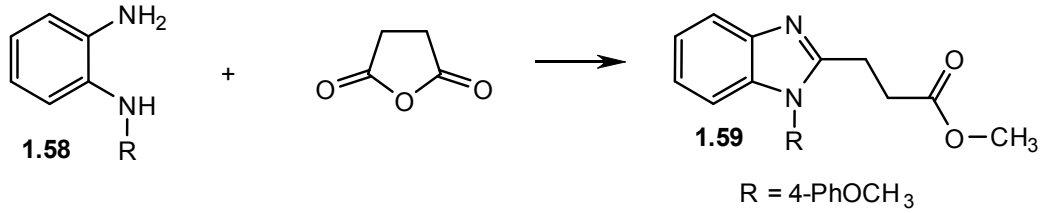

Fig. 16. The single-reactor method for the synthesis of methyl 3-(1-(4-methoxyphenyl)-1H-benzo[d]imidazol-2-yl)propionate

methods were used.

The previous part of this review shows that anhydro-derivatives dicarboxylic acids with sterically adjacent carboxyl groups in the reactions of o-phenylenediamine (1.7) can form benzimidazolil-2-alkyl(aryl)carboxylic acids or the corresponding cyclic imides. In some cases, the structure of reaction products was debatable because of the lack of evidence base. In addition, there is no information in the literary sources about the effect of the conditions for conducting reactions on the structure of the obtained compounds. Nevertheless, Khalil et al. [22] showed that the variation of the conditions for conducting the reaction leads to the formation of the predominant one of the possible products. Thus, the reaction of o-phenylenediamine (1.7) with cyclic anhydride of 9,10-dihydro-9,10-etanoantratsen-11,12-dicarboxylic acid in dimethylformamide or a mixture of dioxane-pyridine results in the formation of 2-(2-aminophenyl)-3a, 4,9,9a-tetrahydro-4,9-benzobenz[f]izoindolo-1,3-dione (1.63). At the same time, interaction of above-mentioned initial compounds in glacial acetic acid in presence of equimolar quantity of sodium acetate yields 12-(1-acetyl-1H-benzimidazole-2-yl)-9,10-dihydro-9,10-ethanoanthracene-11-carboxylic acid (1.62, Fig. 18). Authors consider that ability of the reaction to flow in two ways, depending on the nature of the solvent caused by shifting of tautomeric equilibrium (A and A') of intermediate. The structure of the synthesized compounds is confirmed by IR-, NMR-, mass-spectra.

The study of the peculiarities and conditions of the reaction of o-phenylenediamine (1.7) with camphoric anhydride was carried out by scientists from the National Pharmaceutical University (Kharkiv, Ukraine) [23]. This work is of particular interest, since there are two similar by reactivity, but different by the steric properties electrophilic centers in the indicated cyclic anhydride. According to the high-performance gas-liquid chromatography, the interaction of the reagents, mentioned above, in boiling toluene leads to the formation of a mixture of 3-(1H-benzo[d]imidazol-2-yl)-1,2,2-trimethyl-cyclopentanecarboxylic acid (1.65) and 3-(1H-benzo[d]imidazol-2-yl)-2,2,3-trimethylcyclo-pentanecarboxylic acid (1.67) (Fig. 19). The authors suggested that a decrease in the reaction temperature from 118^{0}C to 100^{0}C could lead to a nucleophilic attack occurring exclusively at a less sterically hindered carbon atom. The practical implementation of such changes showed that the content of the minor component (1.67) of the mixture was decreased from 15% to 4%. A further decrease in temperature of the reaction medium to 80^{0}C led to the desired result: the formation of exclusively 3-(1H-

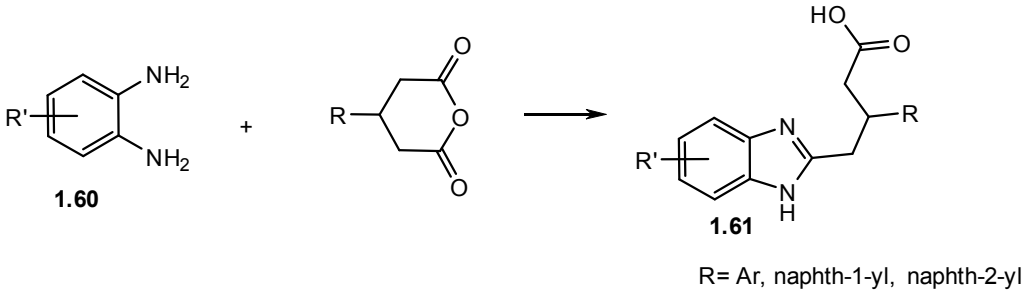

Fig. 17. The approach to the synthesis of combinatorial libraries 4-(1H-benzimidazole-2-yl)-3-arylbutanoic acids

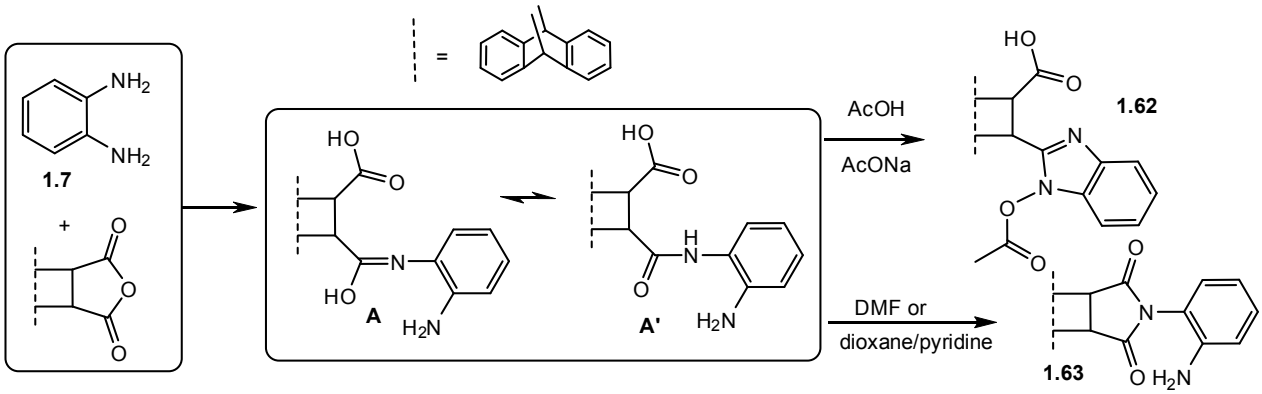

Fig. 18. The peculiarities of the reaction of o-phenylenediamine with 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid anhydride

benzo[d]imidazol-2-yl)-1,2,2-trimethylcyclopentanecarboxylic acid (1.65).

Amides of α-aminoacids and their derivatives in reactions with cyclic anhydrides of dicarboxylic acids

Barton et al. [24] studied the reactions of 2,2-disubstituted 2-aminoacetamides (1.68) with anhydrides of phthalic, pyridine-2,3-dicarboxylic and quinoline-2,3-dicarboxylic acids, as well as with their derivatives. It has been established that the interaction of phthalic anhydride with 2-amino-2,3-dimethylbutyramide results in the formation of 2-(4-isopropyl-4-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl)benzoic acid (Fig. 20). Instead, a similar reaction with 4-methylphthalic anhydride was reported to form two isomeric products (1.69 and 1.70), which was proven by HPLC method. It should be noted that the authors described these substances, but did not separate them.

In the case of the use of pyridine-2,3-dicarboxylic acid anhydrides, the reaction proceeds mainly with the formation of one product 1.72 (Fig. 20). The exception is the reaction of pyridine-2,3-dicarboxylic anhydride with 2-amino-2,3-dimethylbutyramide in acetonitrile and subsequent cyclization in sodium hydroxide solution, which leads to the formation of 2-(4-isopropyl-4-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl)-nicotinic acid (1.72, 90%) and isomeric pycolinic acid (1.71, 10%). In all other cases, the reaction of substituted pyridine-2,3-dicarboxylic acid anhydrides with 2,2-disubstituted 2-aminoacetamides was accompanied by the formation of corresponding derivatives of nicotinic acid. Anhydrides of quinoline-2,3-dicarboxylic acid with 2,2-disubstituted 2-aminoacetamides formed derivatives of 2-(4-isopropyl-4-methyl-5-oxo-4,5-dihydro-1H-

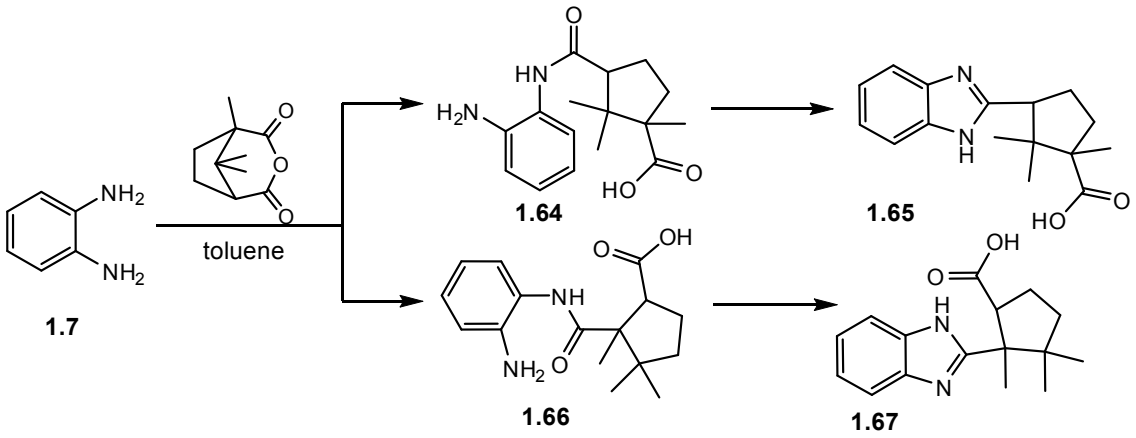

Fig. 19. The features of the reaction of o-phenylenediamine (1.7) with camphoric anhydride

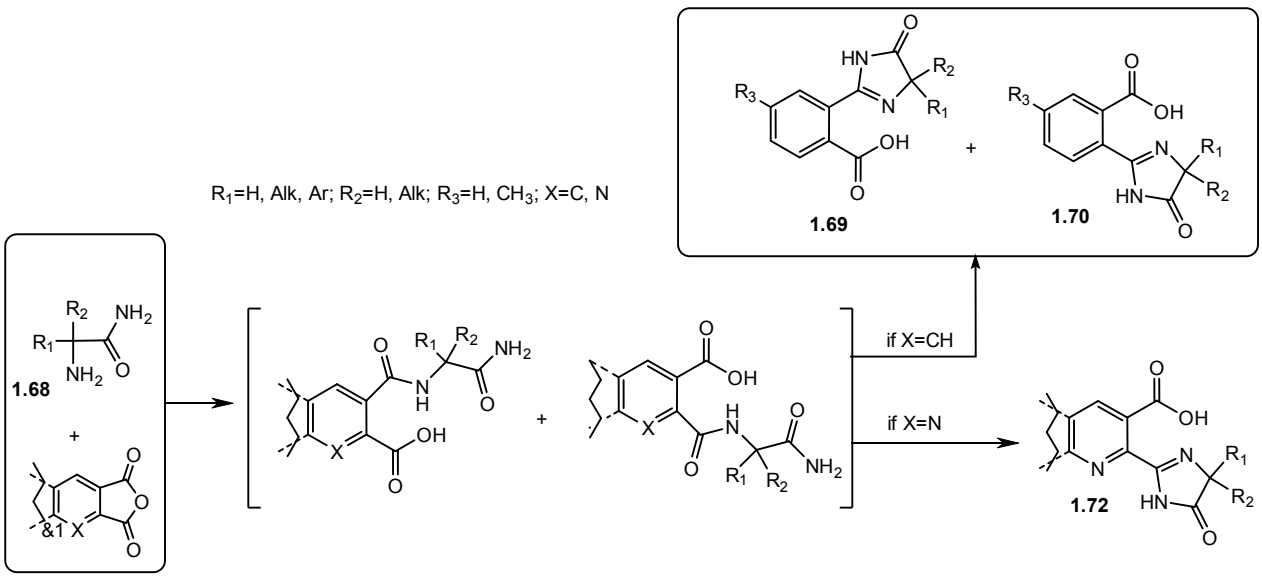

Fig. 20. The interaction of 2,2-disubstituted 2-aminoacetamides with phthalic, pyridine-2,3-dicarboxylic and quinoline-2,3-dicarboxylic acid anhydrides

imidazol-2-yl)quinoline-3-carboxylic acid. In further studies [25,26], there are the extended structural series of similar derivatives (1.72) of nicotinic acid with the imidazole fragment in a molecule.

The next stage in the continuation of these works is the synthesis of chiral imidazolinones that have R-configuration [27], since it has been found that R-forms show higher herbicidal activity compared to the corresponding racemic mixtures. The target R-imidazolinones (1.74) were prepared directly from (R)-2-amino-2,3-dimethylbutyronitrile (1.73) in anhydrous nonpolar solvents (Fig. 21). In this case, the reaction proceeds with absolutely complete preservation of enantiomeric purity.

Los, while continuing the study on the modification of structures 1.69, 1.70, obtained thioanalogues which are similar in structure to the imidazole cycle [28]. The author showed that the interaction of phthalic anhydride with 2-amino-2,3-dimethylthiobutamide (1.75) leads to 1.76 (Fig. 22). However, similar reaction with 4-fluorophthalic anhydride resulted in two intermediates (A and B).

It should be noted that the author did not conduct the separation and study of these intermediates by any physical and chemical methods. According to the authors data, only one substance, 3-fluoro-2-(4-isopropyl-4-methyl-5-thioxo-4,5-dihydro-1H-imidazol-2-yl)benzoic acid (1.77), was isolated as a product in the further cyclization of A and B mixture.

Amidines in reactions with cyclic anhydrides of dicarboxylic acids

An example of microwave-assisted reaction of dicarboxylic anhydrides with binucleophiles is described in the paper [29]. The authors obtained 3-[3-(2-pyridinyl)-1H-1,2,4-triazol-5-yl]propanoic acid (1.79) by microwave irradiation of a mixture of 2-pyridinecarbohydrazonoamide (1.78) and succinic anhydride in dimethylacetamide (Fig. 23). Reaction requires the atmosphere of nitrogen to prevent the possible oxidation of compound 1.78.

A rather unusual class of 1,4-NCCN-

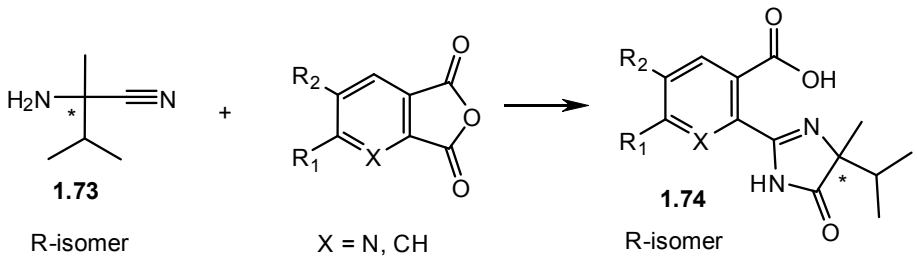

Fig. 21. Synthesis of chiral imidazolinones

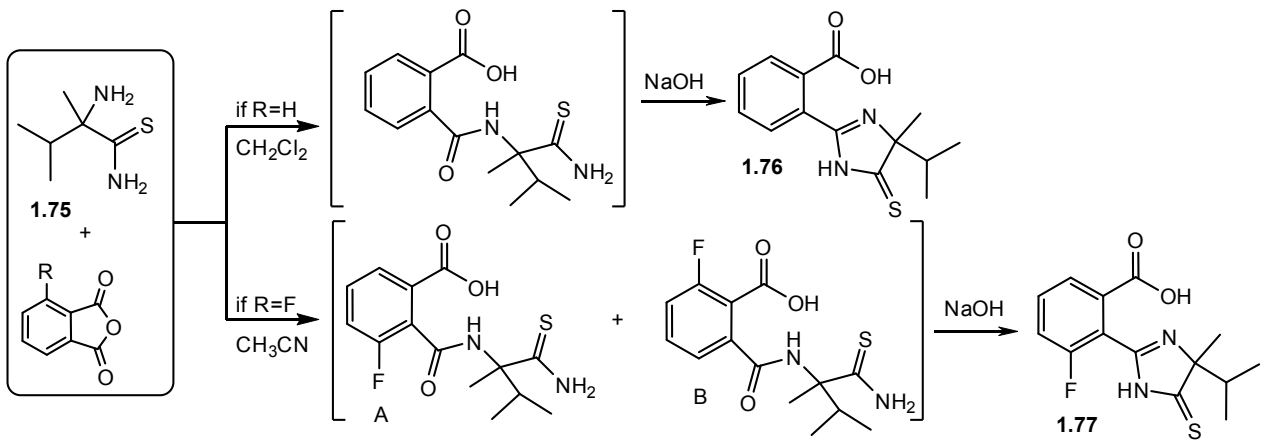

Fig. 22. Synthesis of 3-R-2-(4-isopropyl-4-methyl-5-thioxo-4,5-dihydro-1H-imidazol-2-yl)benzoic acid

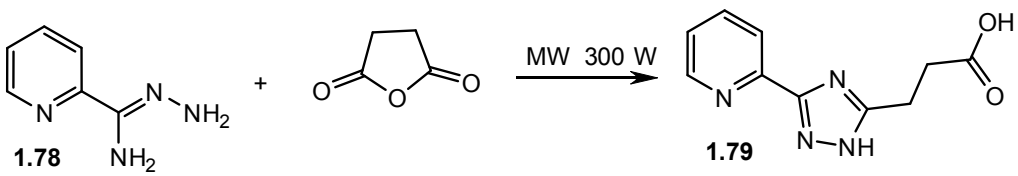

Fig. 23. Microwave synthesis of 3-[3-(2-pyridinyl)-1H-1,2,4-triazol-5-yl]propanoic acid

binucleophiles was used as an initial substance by Matschke et al. [30] in a study devoted to the search of a new pH-sensitive dyes among 4H-imidazoles. Thus, the interaction of bis-(tolyl)oxalamidine (1.80) with the anhydrides of phthalic and naphthalene-1,8-dicarboxylic acids in the conditions of basic catalysis results in the formation of 2-[5-(tolylamino)-4-(tolylimino)-4H-imidazole-2-yl]arylcarboxylic acids with low yields (1.81, 1.82, Fig. 24). The substances obtained are the promising pH- and red/ox-colorants.

An example of the study of the relationship between the reaction conditions and the products of the interaction of 1,4-NNCN-binucleophiles with cyclic anhydrides, which are derivatives of dicarboxylic acids with sterically coupled carboxylic groups, is the work [31]. The authors note that refluxing of N^3-phenylbenzamidrazone (1.83) with cis-1,2-cyclohexanedicarboxylic anhydride in toluene for 6 hours leads to the formation of a cyclic imide 1.84 (Fig. 25). At the same time, cyclocondensation to 2-(4,5-diphenyl-4H-[1,2,4]triazol-3-yl)cyclohexanecarboxylic acid (1.85) was conducted at room temperature in toluene.

It is important that, unlike most previous publications, the complex of physical and chemical methods (IR-, NMR-spectroscopy, and X-ray diffraction analysis) as well as quantum-mechanical calculation were used to verify the structure of substance (1.84 and 1.85).

The continuation of work [31] is a publication [32] in which the reaction of N^3-phenyl(pyridin-2-yl)carbohydrazonamide (1.86) with itaconic anhydride was studied. The authors showed that the interaction of the starting substances in diethyl ether over a seven day period leads to 2-{[4-phenyl-5-(pyridin-2-yl)-4H-1,2,4-triazol-3-yl]methyl}acrylic acids (1.87, Fig. 26). While mixing the same reagents in anhydrous ether for 2 hours, followed by boiling the resulting intermediate in a sodium hydroxide solution for 2 hours, leads to 2-methyl-3-[4-phenyl-5-(pyridin-2-yl)-4H-1,2,4-triazol-3-yl]acrylic acid (1.88). The nature of reaction intermediate (A) and the possibility of the transformation of compound 1.87 to 1.88 were discussed as well.

The most extensive study of the interaction of N-substituted amidrazones with cis-1,2-cyclohexanedioic anhydride is the work [33], in which the effects of amidrazone structure and the conditions on the result of the reaction were studied (Fig. 27). The study showed that, when amidrazones with phenyl and pyridinyl radicals (1.86 and 1.89) were used in the reaction, the result of their interaction with anhydride in diethyl ether is a mixture of acylation products (1.90 and 1.91) with the corresponding isoindoline derivatives (1.92 and 1.93). A similar interaction of amidrazones containing substituents with pronounced electron-acceptor properties (1.94 and 1.95) leads to the formation of the corresponding acylation products (1.96 and 1.97), i.e. the reaction is not accompanied by heterocyclicization. The introduction of the activated aromatic system into the N-position of the amidrazone (1.98 and 1.99) leads to the formation of a triazole system, namely the formation of 2-(4-R-5-R'-4H-1,2,4-triazol-3-yl)cyclohexanecarboxylic acids (1.100 and 1.101).

For initial compounds that contain phenyl

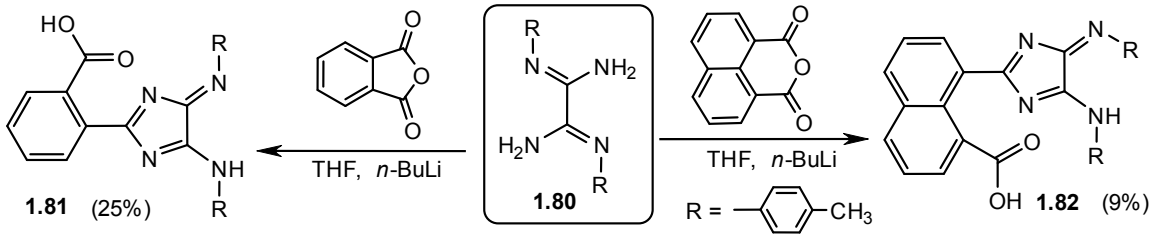

Fig. 24. Synthesis of 2-[5-(tolylamino)-4-(tolylimino)-4H-imidazol-2-yl]arylcarboxylic acids, promising pH- and red/ox-colorants

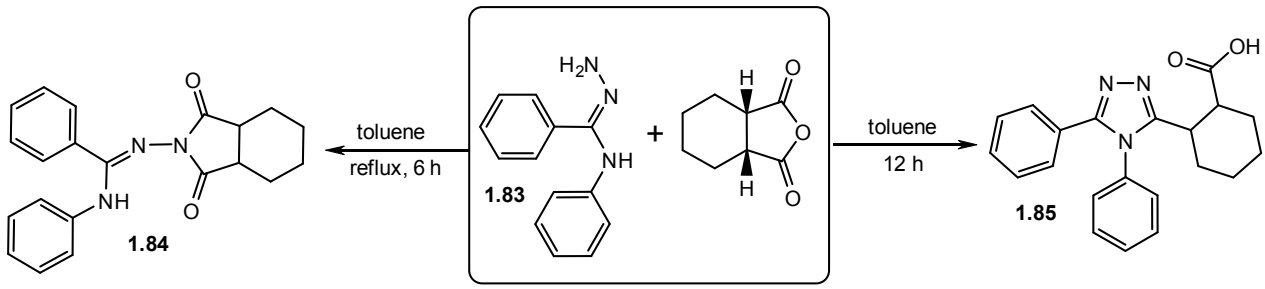

Fig. 25. Interaction of N^3-phenylbenzamidrazone with cis-1,2-cyclohexanedicarboxylic acid anhydride

substituent (1.83) or a combination of phenyl and p-nitrophenyl substituents (1.102), reaction gave corresponding N-(1,3-dioxooctahydro-2H-isoindol-2-yl)-N'-arylbenzocarboximidamides 1.84 and 1.103. Reaction between compounds 1.83, 1.86 and 1.89 and above-mentioned anhydride in the more harsh conditions (refluxing in toluene for 6 hours) led to the formation of corresponding isoindole derivatives 1.84, 1.92 and 1.93. It is important to note that the interaction of N-phenylbenzhydrazonamide (1.83) with cis-1,2-cyclohexanedicarbonic anhydride in toluene at ambient temperature leads to the formation of 2-(4,5-diphenyl-4H-1,2,4-triazole-3-yl)cyclohexanecarboxylic acid (1.85), despite the fact that the corresponding isoindole 1.84 is formed under refluxing in toluene or ether (Fig. 27).

The foregoing works concerned the use of amidrazones as 1,4-NNCN-binucleophiles. However, it should be noted that such studies are not numerous. Despite the fact that these compounds

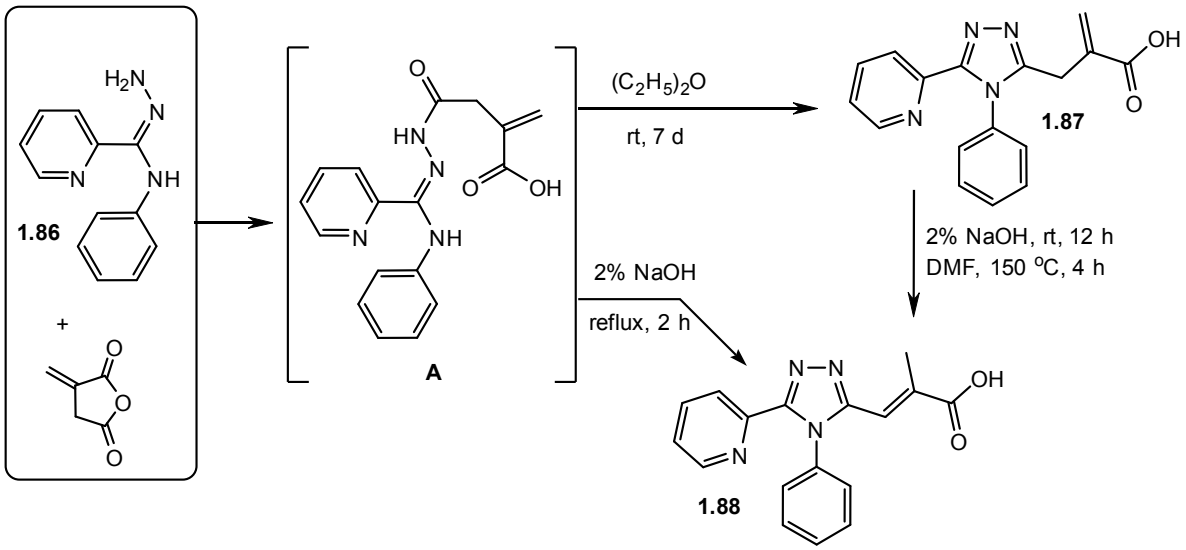

Fig. 26. Peculiarities of the reaction of N[3]-phenyl-(pyridine-2-yl)-carbodizazonamide with itaconic anhydride

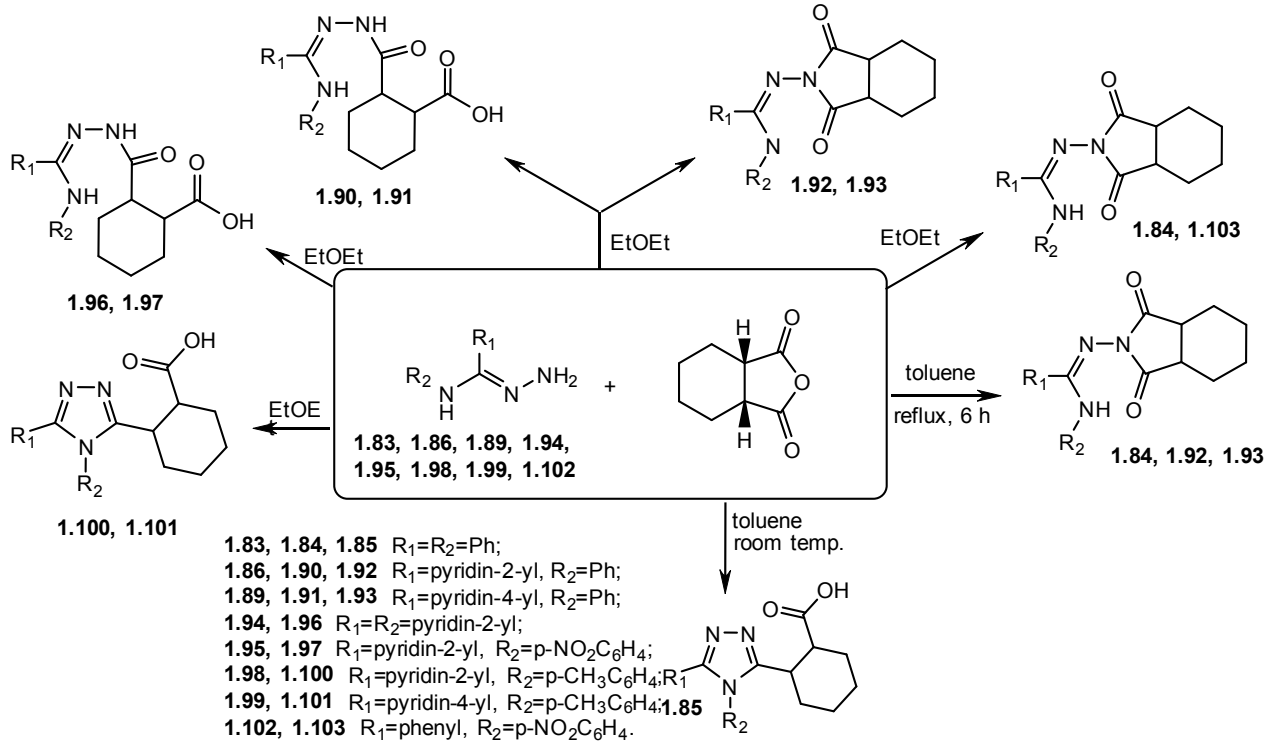

Fig. 27. Interaction of N-substituted amidrazones with cis-1,2-cyclohexane-dicarboxylic anhydride

can be highly effective synthons for preparation of various heterocyclic systems, their practical application is limited in view of their low synthetic availability.

Hydrazine derivatives in reactions with cyclic anhydrides of dicarboxylic acids

Krezel [34] used imidazolidine-2-ylidenehydrazine hydroiodide (1.104) and N-(4,5-dihydro-1H-imidazol-2-yl)-N-methylhydrazine hydroiodide (1.106) as initial substances to obtain heterocyclic systems that combine 1,2,4-triazole and imidazole fragments in their structure. Within the framework of this research, the behavior of the indicated hydrazines towards the various acylating reagents was investigated. It was found that it was possible to synthesize the corresponding imidazo[2,1-c][1,2,4]triazoles (1.105 and 1.107) only when using the succinic anhydride acylating agent (Fig. 28). The reaction was carried out in an acetic acid medium at heating for 14 hours. The reaction products were isolated with the yields of 57% and 46% for substances 1.105 and 1.107, respectively. The structures of the obtained compounds were confirmed by IR- and ^{1}H NMR-spectroscopies. Thus, the ^{1}H NMR-spectrum of compound 1.105 exhibited signals from protons of the corresponding aliphatic groups and methylene groups of the imidazole fragment (2.85 and 3.83 ppm), as well a broad diprotonic singlet heterocycle NH-group at 9.02 ppm. In the ^{1}H NMR-spectrum of compound 1.107, along with the signal of the methyl group at 3.52 ppm, signals from the methylene groups of the imidazole (3.87 ppm) and alkylcarboxyl (2.82 ppm) fragments were observed.

Karpenko and Kovalenko [35] described the interaction of 4-hydrazinoquinazoline with cyclic anhydride of dicarboxylic acids. The authors found out that the reaction of the starting 4-hydrazinoquinazoline (1.108) with cyclic anhydrides of dicarboxylic acids in the acetic acid medium has a number of features (Fig. 29), and the direction of its flow is determined both by the conditions and the structure of the initial anhydride. Thus, the interaction with succinic and glutaric anhydrides is accompanied by cyclocondensation with formation of the corresponding triazoloquinazoline (1.109 and 1.110). At the same time, cyclic anhydrides of dicarboxylic acids with rigid molecular structure (endic, camphoric, phthalic anhydride and its hydrogenated analogs) in reactions with compound 1.108 form the corresponding cyclic 4-imidoaminoquinazoline 1.111–1.115 (Fig. 1.29).

The evaluation of the structure of synthesized substances was carried out based on spectral data. Thus, a paramagnetic shift of the singlet proton H-5 of the triazoloquinazoline system in low fields (9.52–9.27 ppm) was observed in the

^{1}H NMR-spectra of compounds 1.109 and 1.110. An overlapping of H-2 and H-5 protons is observed in the form of a multiplet (1.111) or a doublet (1.112 and 1.113) at 8.39–8.22 ppm in the ^{1}H NMR-spectra. In the case of compound 1.115, these signals are observed separately at 8.46 ppm (H-5) and 8.29 ppm (H-2).

Refluxing of 1.116 with anhydride of 2,2-dimethylsuccinic acid in dioxane for 2 hours leads to the formation of [1,2,4]triazolo[4,3-a]pyridine system [36] (Fig. 30).

A similar structure for compound 1.116 is in

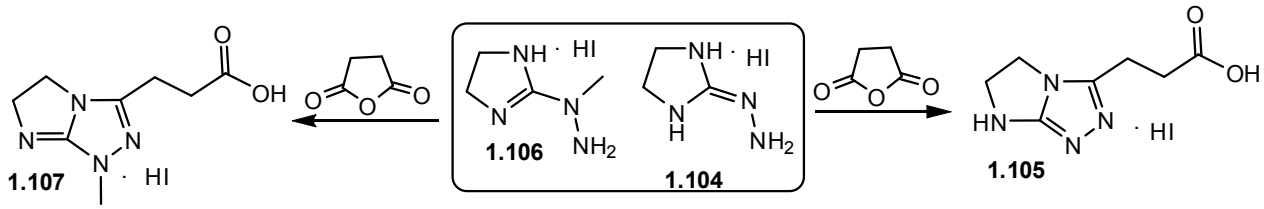

Fig. 28. The interaction of 2-hydrazino-1H-imidazolines with succinic anhydride

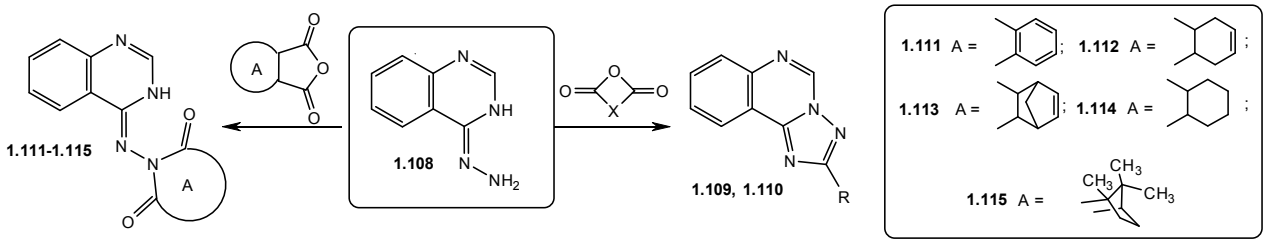

Fig. 29. The features of interaction of 4-hydrazinoquinazoline with anhydrides of dicarboxylic acids

some way 2-hydrazinyl-3-phenyl-quinoxaline (1.118), on the basis of which an original 1,2,4-triazolo[4,3-a]quinoxaline system (1.119) was formed by interaction with succinic anhydride in glacial acetic acid [37]. The reaction of compound 1.118 with phthalic anhydride in glacial acetic acid medium was studied. The authors claimed that the product of this interaction was 2-(4-phenyl-1,2,4-triazolo[4,3-a]quinoxalin-1-yl)benzoic acid (1.120). However, it should be noted that the researchers did not use the ^{1}H NMR-spectroscopy to confirm the structure of compound 1.120 and they did not consider the possibility of formation of the corresponding cycloimide (Fig. 31).

1,4-Binucleophiles of another structure in reactions with cyclic anhydrides of dicarboxylic acids

Schipper and Day [38] carried out the synthesis of 3-(1H-imidazo[4,5-b]quinoxalin-2-yl)propanoic acid by the interaction of quinoxalin-2,3-diamine (1.121) with succinic anhydride in pyridine medium (1.122, Fig. 32). Purification of the reaction product was carried out by crystallization from 70% ethanol and the yield was 87%.

Noteworthy is the work by Bukowski and Janowiec [39], in which the possibility of the formation of two polymorphic forms (1.124a and 1.124b) of product of interaction between 2,3-diaminopyridine (1.123) and succinic anhydride at different temperatures was stated (Fig. 33). It was established that fusing of the starting substances at temperatures 145–150^{0}C resulted in 3-(3H-imidazo-[4,5-b]pyridine-2-yl)propanoic acid (1.124a) while reaction at 195–200^{0}C yielded 1.124b. The form 1.124a was also obtained by refluxing of the starting substances in the xylene for 1 hour. The publication also noted that polymorphic form 1.124a was transformed into the form 1.124b at temperatures 195–200^{0}C. It should be noted that N-(2-amino-pyridin-3-yl)succinamide (1.125) was considered as possible product of compound 1.123 acylation. Subsequently, this hypothesis was rejected based on the data of spectral studies (IR-, ^{1}H NMR-spectroscopy, and mass-spectrometry), since the compounds 1.124a and 1.124b, which were obtained, had identical analytical data. With the aim of proving the structure of compounds 1.124a and 1.124b, the authors developed an alternative method of synthesis, namely, the interaction of 2-nitropyridine-3-amine

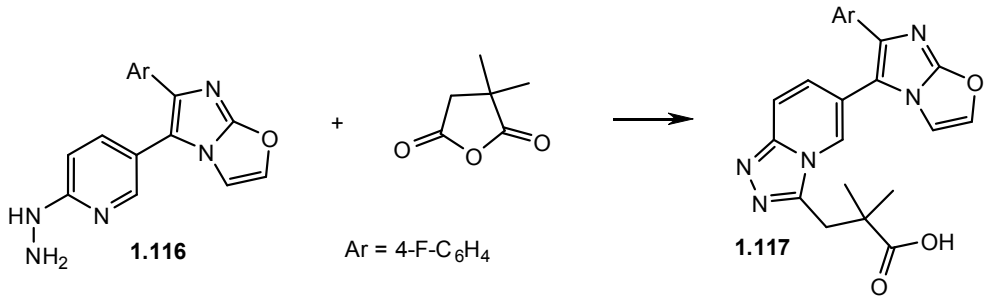

Fig. 30. The synthesis of 3-{6-(6-(4-fluorophenyl)imidazo [2,1-b]oxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl}-2,2-dimethylpropanoic acid

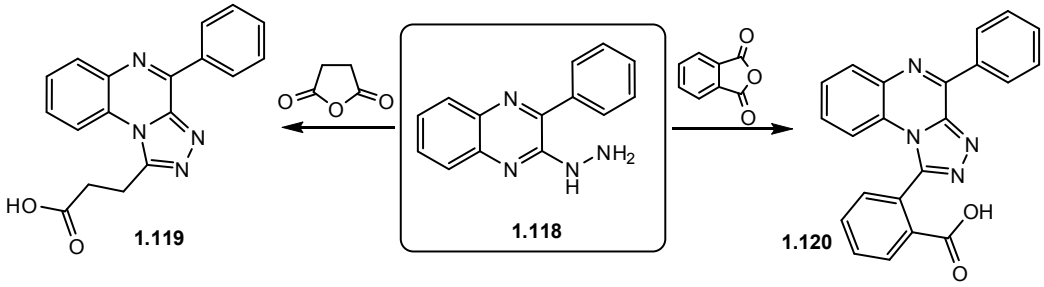

Fig. 31. The interaction of 2-hydrazino-3-phenylquinoxaline with succinic and phthalic anhydrides

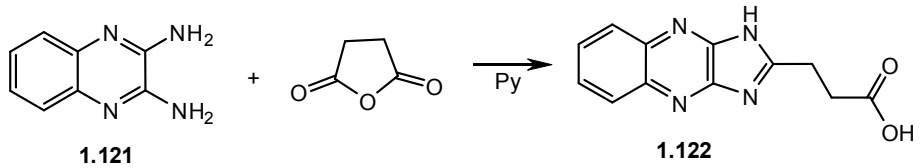

Fig. 32. The interaction of quinoxalin-2,3-diamine with succinic anhydride

(1.128) with succinic anhydride (Fig. 33). The resulting lactam 1.129 was hydrolyzed, and compound 1.130 was reduced to a synthesis of N-(2-aminopyridin-3-yl)succinamide (1.125). In this case, compound 1.125 had different spectral characteristics with reference to 1.124a and 1.124b, which is also an argument to reject its formation in the case of synthesis of 3-(3H-imidazo[4,5-b]pyridin-2-yl)propanoic acid (1.124a) at temperatures of 145–150^{0}C. It is important that 1.125 is converted into a polymorphic form of 1.124b at the temperatures of 190–200^{0}C. In addition, esterification of 1.124a and 1.124b yielded the same product (1.126) as well as formed lactam 1.127 while heating in acetic anhydride medium.

Bukowski and Janowiec [39] conducted the synthesis of 1- and 3-monomethylsubstituted 3-(3H-imidazo[4,5-b]pyridin-2-yl)propanoic acid (1.133 and 1.134, Fig. 34). For the synthesized compounds and a number of their functional derivatives (esters, amides, hydrazides, nitriles, etc.), their properties and physicochemical characteristics were studied.

The cyclocondensation of 4,5,6-triaminopyrimidine (1.135) with glutaric anhydride was investigated [40] (Fig. 35). It ws shown that the result of this reaction is the formation of the corresponding 4-(6-aminopurin-8-yl)butanoic acid (1.136). The selective alkylation was carried out by 1.136 alkylhalides in DMF in position 3. The possibility of the formation of compounds 1.137–1.119 was explained by the existence of compound 1.136 as a mixture of tautomeric forms. The structure of the alkylation products (1.137–1.139) was proved by the method of ^{1}H NMR-spectroscopy and X-ray diffraction analysis.

Chernyshev et al. [41] studied the reaction of aminoguanidine hydrochloride 1.140 with succinic acid and its anhydride (Fig. 36). It was shown that the mixture of 3-(5-amino-1H-1,2,4-triazol-3-yl)propanoic acid (1.141) and 3,3'-(ethane-1,2-diyl)-bis(1H-1,2,4-triazol-5-amine) (1.142) was obtained in the above-mentioned reactions when succinic acid

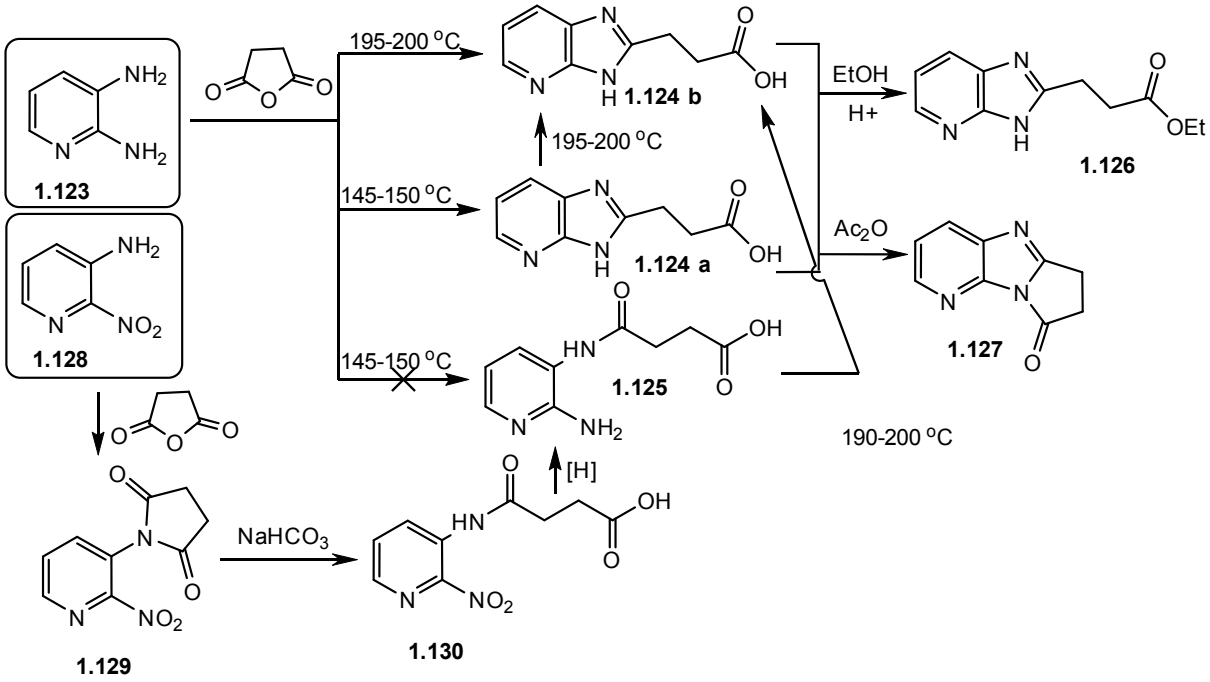

Fig. 33. The main approaches to the synthesis of polymorphic forms of 3-(3H-imidazo[4,5-b]pyridin-2-yl)propanoic acid and its derivatives

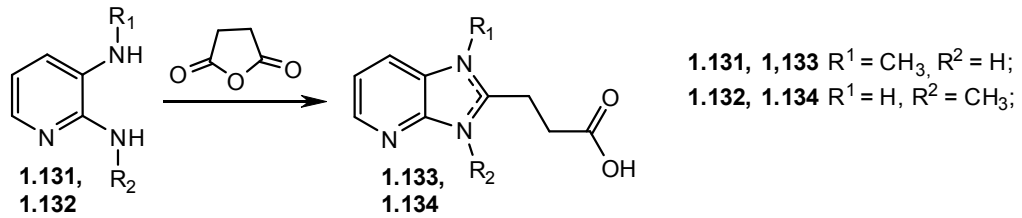

Fig. 34. The interaction of 1- and 3-substituted monomethyl substituted 2,3-diaminopyridine with succinic anhydride

was an electrophilic reagent. It was established that only substance 1.141 with high yields is formed precisely when the aminoguanidine hydrochloride is fused with succinic anhydride. The structure of the obtained compounds was proven by the methods of ^{1}H-, ^{13}C-, IR-spectroscopies and mass-spectrometry. In the ^{1}H NMR-spectrum of compound 1.141, the characteristic signals of the alkylcarboxyl moiety are present at 2.54, 2.62 and 11.89 ppm. The mass-spectrum exhibits a low-intensive molecular ion (27%). The main direction of fragmentation is decarboxylation of this substance, which causes the appearance of the most intense ion (100%), which is characteristic of carboxylic acids. Other signals that are present in the mass-spectrum are due to the fragmentation of the triazole cycle. It should be noted that this publication proves the advantage of using cyclic anhydrides of dicarboxylic acids in cyclocondensation reactions in comparison with the corresponding carboxylic acids.

Heterocyclization on the basis of 1,5-NCCCN-binucleophiles and cyclic anhydrides of dicarboxylic acids

The analysis of literature data showed that publications devoted to the study [5+1]-cyclocondensation involving cyclic anhydrides of dicarboxylic acids are not numerous as compared with the papers that were considered in the previous part of the review.

Amide of anthranilic acid and its derivatives in reactions with cyclic anhydrides of dicarboxylic acids

Usifoh [42] developed a method for the synthesis of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)alkylcarboxylic acids (1.144 and 1.145) via the interaction of anthranilic acid amide (1.143) with succinic and glutaric anhydrides. It was shown that the reaction was readily realized by refluxing of the starting substances in toluene medium, with the yields of the target compounds being from 80% to 85% (Fig. 37).

A slightly different approach to the formation of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)carboxylic acids (1.144, 1.149 and 1.152) was used in paper [43]. In this publication, the mentioned class of compounds was obtained by a two-step synthesis, which included preliminary condensation at room temperature of the starting material 1.143 with the corresponding anhydrides, followed by cyclization of the formed intermediates 1.146, 1.148 and 1.151 by refluxing in acetic anhydride in the presence of sodium acetate (Fig. 38).

The structure of the synthesized substances was proven by ^{1}H NMR-spectroscopy. It should be noted that the ^{1}H NMR-spectra of compounds 1.144, 1.149 and 1.152 showed the presence of a broad singlet of the proton of the NH-group, which appears as a

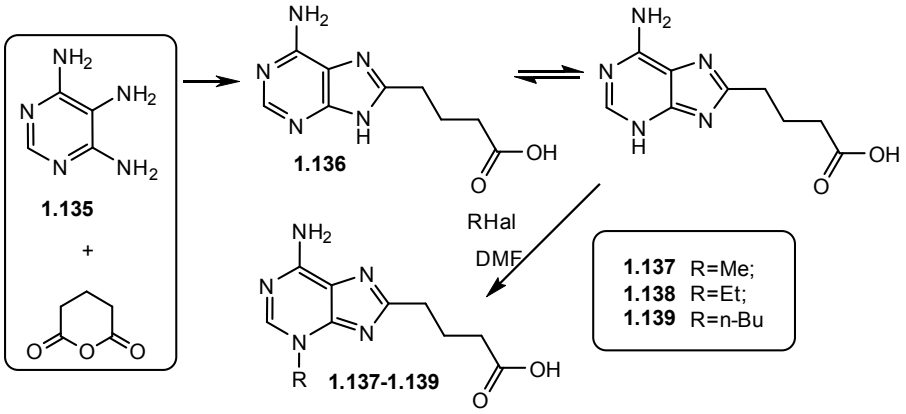

Fig. 35. The interaction of 4,5,6-triaminopyrimidine with glutaric anhydride

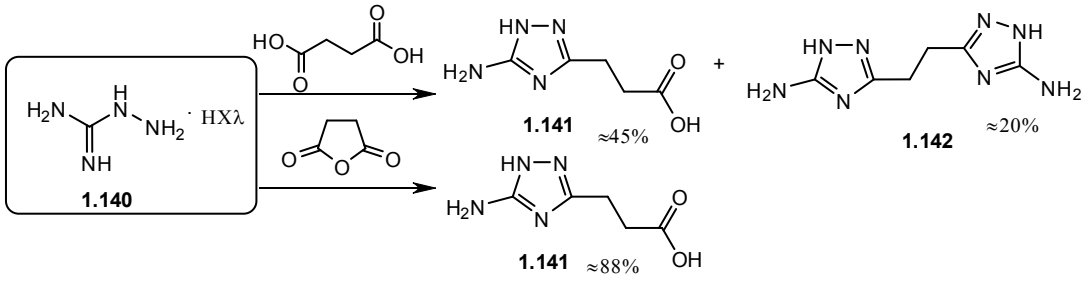

Fig. 36. The features of the interaction of aminoguanidine hydrochloride with succinic acid and its anhydride

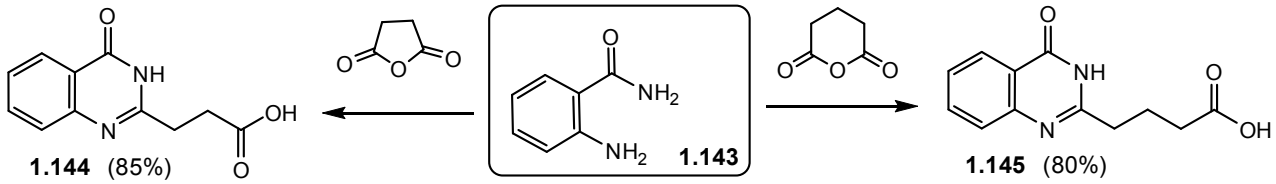

Fig. 37. The method of synthesis of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)alkylcarboxylic acids

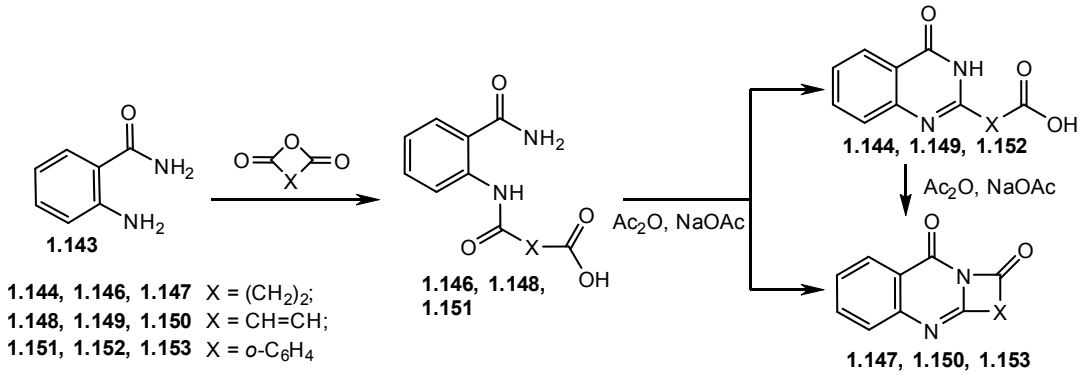

Fig. 38. The interaction of anthranilic acid amide with anhydrides of dicarboxylic acids

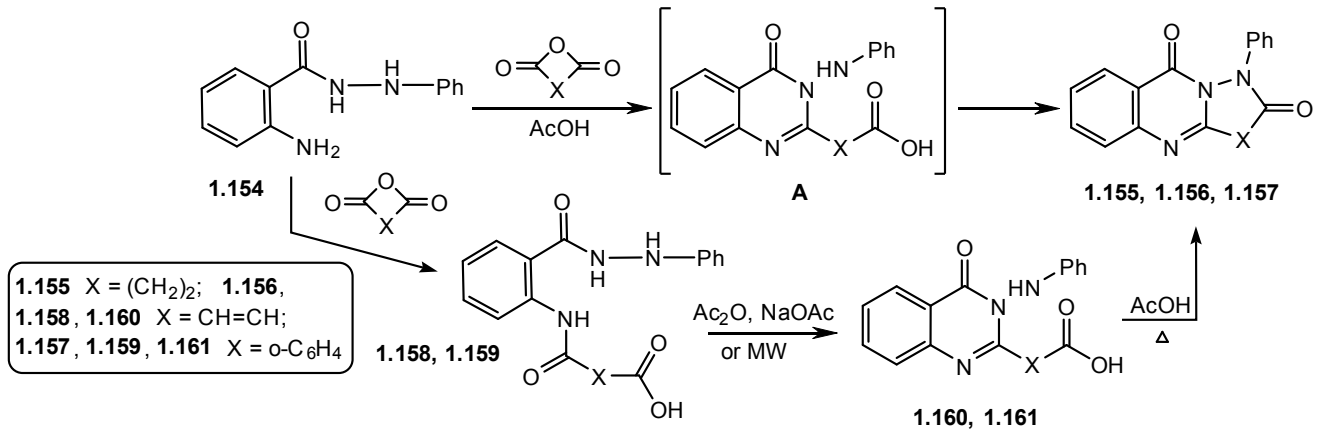

Fig. 39. The methods of synthesis of pyridazino- and phthalazinoquinazolines

result of the formation of the 4-oxoquinazoline system. The application of this approach allowed researchers to identify the relevant intermediate reaction products and expand the combinatorial library of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-carboxylic acids.

Subsequently, the scientists used a similar approach to the formation of a number of condensed derivatives of quinazoline [44]. In this case, nucleophile 2-N-phenylhydrazide of anthranilic acid (1.154) was selected as a starting substance. It was shown that the interaction of nucleophile with succinic, maleic and phthalic anhydrides in acetic acid medium under refluxing leads to the formation of the corresponding pyridazino- (1.155 and 1.156) and phthalazinoquinazolines (1.157) (Fig. 39). It should be noted that the intermediates of this reaction are the corresponding (3-anilino-4-oxo-3,4-dihydroquinazolin-2-yl)carboxylic acids (A) what is proven by stepwise synthesis.

The method for the formation of quinazoline systems via condensation of anthranilic (1.143) and 5-chloroantaranilic (1.162) acids amides with anhydride of 3-(4-chlorophenyl)glutaric acid is described in the work [21] (Fig. 40). The refluxing of the named substances in toluene resulted in the formation of 3-(4-chlorophenyl)-4-(4-hydroxyquinazolin-2-yl)butanoic acid (1.163) and its 6-chloro-substituted derivative (1.164).

1,5-Binucleophiles of another structure in reactions with cyclic anhydrides of dicarboxylic acids

Sachs [45] reported the cyclocondensations on the basis of 1,8-diaminonaphthalene (1.165). It was shown that the interaction of succinic anhydride with

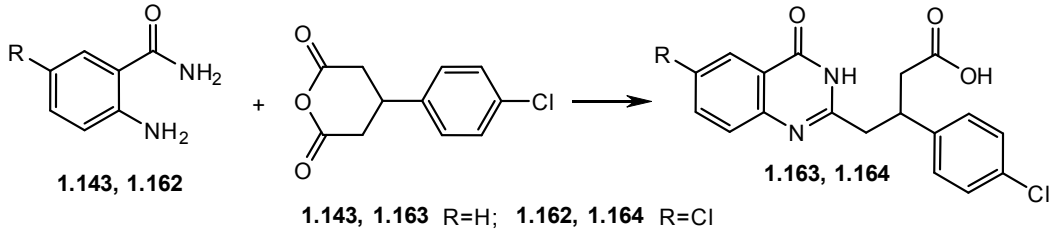

Fig. 40. The interaction of anthranilic and 5-chloroanthranilic acid amides with 3-(4-chlorophenyl)glutaric anhydride

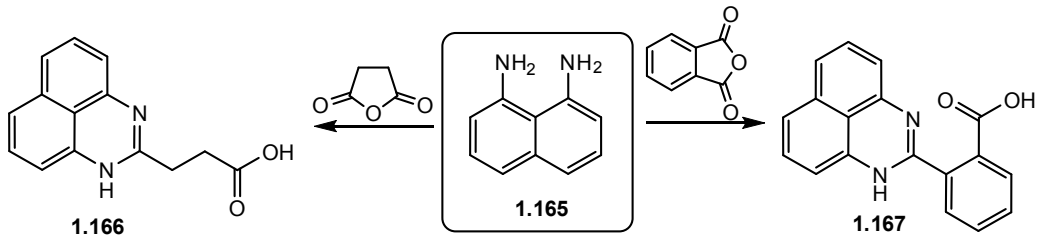

Fig. 41. The basic approaches to the synthesis of 3-(1H-perimidine-2-yl)propanoic and benzoic acids

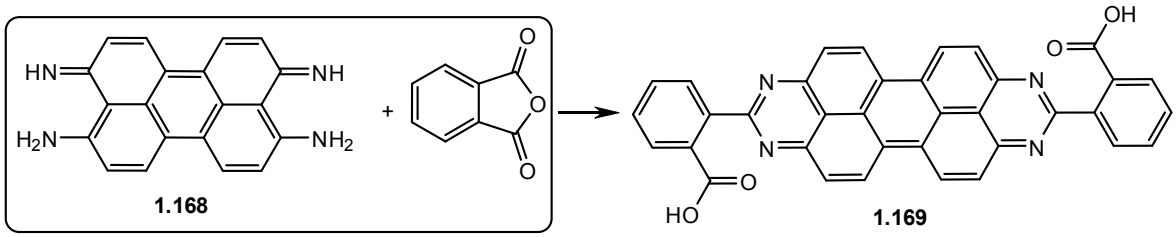

Fig. 42. The method for 2,9-bis-(2-carboxyphenyl)-1,3,8,10-tetraazaperopyrene synthesis

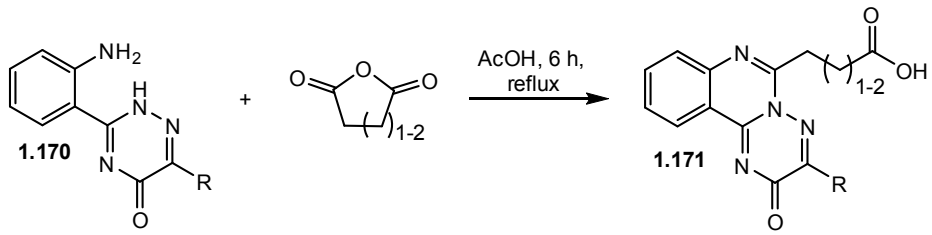

Fig. 43. Preparation of (3-R-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl)alkylcarboxylic acids

1.165 in toluene medium leads to the formation of 3-(1H-perimidine-2-yl)propanoic acid (1.166). In the same work, the reaction of 1.165 with phthalic anhydride was studied. It was shown that 3-(1H-pyrimidine-2-yl)benzoic acid was formed as a result of the above-mentioned reaction (1.167, Fig. 41).

Riehm et al. [46] described the interaction of amine-containing polycyclic aromatic compounds with phthalic anhydride. It was shown that the reaction of 4,9-diamino-3,10-perylenequinondiimine (1.168) with phthalic anhydride in nitrobenzene for 6 hours results in the formation of 2,9-bis-(2-carboxyphenyl)-1,3,8,10-tetraazaperopyrene (1.169) (Fig. 42). The structure of the obtained substances was proved by spectral methods, in particular ^{1}H and ^{13}C NMR spectroscopy. The most informative in this case were ^{13}C NMR spectra. Thus, the characteristic signal of compound 1.169 was a weak field singlet of a carboxyl group at 170.8 ppm.

Voskoboinik et al. [47] studied the reactivity of succinic and glutaric anhydrides towards original 1,5-nucleophiles, namely 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-ones. It was shown that refluxing abovementioned compounds in glacial acetic acid resulted in the formation of previously unknown (3-R-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl)alkylcarboxylic acids (Fig. 43).

Subsequently, the same authors studied the features of reaction between 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-ones and anhydrides of non-symmetrical dicarboxylic acids [48]. It was found that the reaction of compounds 1.170 with anhydrides

of 2-methylsuccinic and 2-phenylsuccinic acids resulted in the formation of mixtures of corresponding acids 1.172 and imides 1.173 (Fig. 44).

The same paper [48] reported the preparative method for synthesis of 1,2,2-trimethyl-3-(3-R-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl)-cyclopentane-1-carboxylic acids (1.174) (Fig. 45). It was evaluated that regioselectivity of reaction between initial compounds 1.170 and anhydride of the non-symmetrical camphoric acid can be achieved by heating of reaction mixture at 80°C for 30 minutes followed by its refluxing for 6 hours.

3-(2-Aminophenyl)-6-R-1,2,4-triazin-5(2H)-ones were studied in reactions towards the phthalic anhydride [49]. It was found that corresponding phthalimides 1.175 were the products of the reaction (Fig. 46).

Biological properties of products of interaction of 1,4- and 1,5-binucleophiles with cyclic anhydrides of dicarboxylic acids

Analysis of the data given in the previous section proves that the cyclocondensation reactions involving 1,4- and 1,5-binucleophiles and dicarboxylic acids anhydrides results in heterocyclic compounds containing pharmacologically valued fragments. Naturally, this fact could not be left without attention of specialists who are engaged in the search for the new biologically active substances. However, it should be noted that the study of biological activity among these substances is still negligible.

The study of the biological properties of products of the interaction of 1,4- and 1,5-binucleophiles with dicarboxylic acids anhydrides was carried out in different directions. In particular, significant amounts of works investigated the influence of these substances on pathogens of infectious diseases. Thus, Chatterjee [8] synthesized benzimidazolyl-2-propionic acid (1.8) and a number of its functional derivatives as promising biologically active substances to search for new substances with antimalarial activity. However, the tested compounds of this type of activity were not detected.

Woolley [50] performed the study on the relationship «structure vs. antibacterial activity» among structural analogues of dimethyldiamino-benzene. However, 3-(5,6-dichloro-1H-benzo-

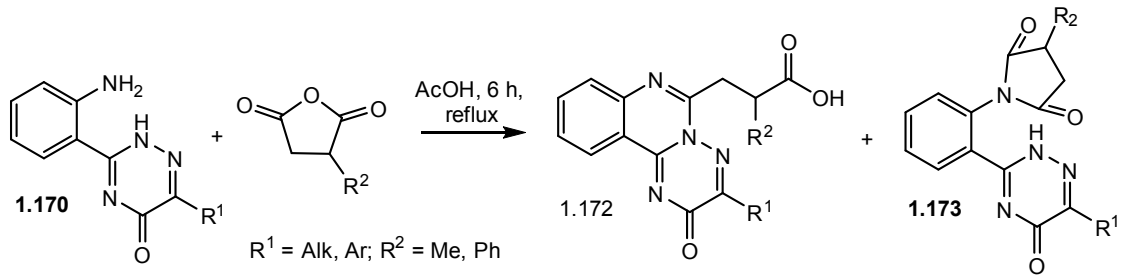

Fig. 44. The features of reaction between 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-ones and anhydrides of non-symmetrical dicarboxylic acids

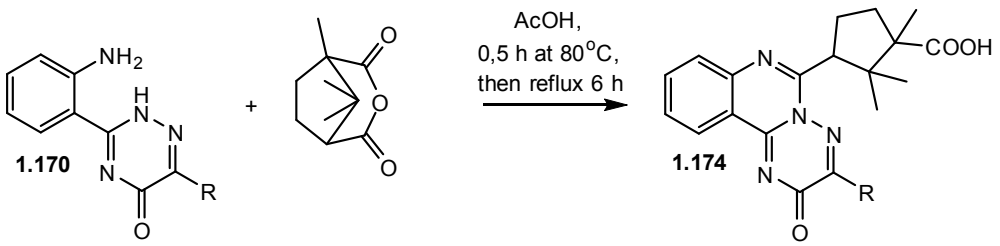

Fig. 45. The features of reaction between 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-ones and camphoric anhydride

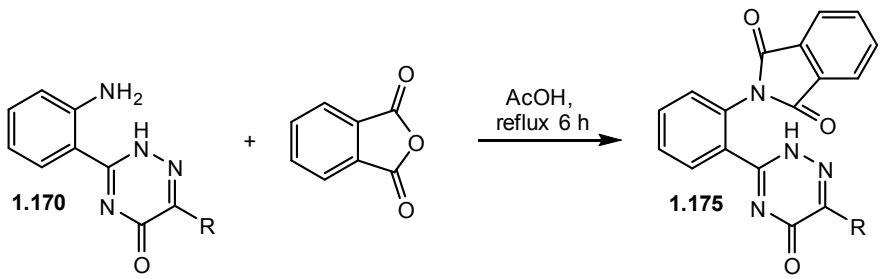

Fig. 46. The features of reaction between 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-ones and phthalic anhydride

[d]imidazol-2-yl)propanoic acid (1.25) showed only moderate antimicrobial activity.

Khalil et al. [22] reported the results of the study of antibacterial activity of o-phenylenediamine (1.7) modification products. In particular, the antimicrobial activity of 12-(1-acetyl-1H-benzimidazole-2-yl)-9,10-dihydro-9,10-etanoantratsen-11-carboxylic acid (1.62) against the strains of both gram-positive (*Bacillus thuringiensis*), and gram-negative (*Escherichia coli*) bacteria was studied. The results showed that the indicated compound exhibited antimicrobial activity against *Bacillus thuringiensis.*

The antimicrobial and antifungal activity of substances produced by condensation N^3-phenylbenzamidrazone (1.83) with cis-1,2-cyclohexanedicarboxylic anhydride under different conditions was investigated in the publication [31]. The study of these types of biological activity was carried out in relation to ten strains of pathogenic and opportunistic microorganisms. It was established that the compound 1.84 revealed a pronounced antibacterial activity (MIC=100 μg/ml) against the strain of *Enterococcus faecalis*, and the compound 1.85 exhibited a pronounced antibacterial activity against the two strains of bacteria (*Yersinia enterocolitica*, *Rhodococcus equi*) and fungi *Candida albicans.* The other types of microorganisms showed a moderate depressant effect compounds (MIC=250–500 μg/ml).

Aiming to continue the study of the antimicrobial and antifungal activity of condensation products of substituted hydrazonoamides with cyclic anhydrides of dicarboxylic acids, Modzelewska-Banachiewicz et al. [32] investigated the effect of 2-{[4-phenyl-5-(pyridin-2-yl)-4H-1,2,4-triazole-3-yl]methyl}acrylic (1.87) and 2-methyl-3-[4-phenyl-5-(pyridin-2-yl)-4H-1,2,4-triazol-3-yl]acrylic (1.88) acids against bacterial and fungal strains. The results showed that the compound 1.87 showed antimicrobial activity against *S. lutea* and *E. faecalis* (MIC_{50}=100 μg/ml), as well as *Y. enterocolitica*, *Nocardia spp.* and *C. albicans* (MIC_{50}=250 μg/ml). The substance 1.88 inhibits the growth of *Y. enterocolitica*, *M. smegmatis*, *Nocardia spp.* and *C. albicans* at the concentration of 250 μg/ml. The publication also notes that the compounds 1.87 and 1.88 do not affect the concentrations, which were studied on the growth of microorganisms such as *E. coli*, *S. aureus* and *P. aeruginosa.*

The purpose of the substantial study [33] was to study antibacterial, antiviral and anti-inflammatory activity among the products of the interaction of N^3-substituted amidrazones with cis-1,2-cyclohexanedicarboxylic anhydride, in particular between 2-(4-R-5-R'-4H-1,2,4-triazol-3-yl)-cyclohexanecarboxylic acids 1.85, 1.100 and 1.101. The greatest effectiveness against both gram-positive (*E. faecalis*, *S. lutea*, *M. smegmatis* and *R. equi*), and gram-negative (*E. coli* and *Y. enterocolitica*) bacteria was found for 2-(5-(pyridine-4-yl)-4-p-tolyl-4H-1,2,4-triazol-3-yl)cyclohexanecarboxylic acid (1.101) for which the MIC value was ranged from 50 to 100 μg/ml. It should be noted that 2-(5-(pyridine-2-yl)-4-p-tolyl-4H-1,2,4-triazole-3-yl)cyclohexanecarboxylic acid (1.100) showed the effectiveness only against gram-positive bacteria. Thus, the growth of *S. lutea* and *Nocardia* was suppressed by the compound 1.100 at the concentrations of 100 and 50 μg/ml, respectively. 2-(4,5-Diphenyl-4H-1,2,4-triazol-3-yl)cyclo-hexanecarboxylic acid (1.85) revealed a moderate activity against *Y. enterocolitica* and *R. Equi* (MIC=100 μg/ml).

The studies of antiviral activity have shown that the compound 1.100 exhibits the antiviral properties. Thus, against encephalomyocarditis virus, the titer reduction was 1.5 units at the concentration of 1.100 equal to 2 μg/ml. Based on the high prospects of this compound as a potential antiviral drug, its cytotoxicity according to the line of CCD-18C0 cells was studied. It was established that the compound being tested exhibited cytotoxic properties at the concentration of 100 μg/ml (about 6.2% survival of intact cells), whereas the compound 1.100 did not practically reveal any cytotoxic actions at the concentration of 2 μg/ml corresponding to the concentration at which antiviral activity was studied (cell survival was about 99.6% with respect to the control).

The study of the effects of synthesized compounds on some important physiological and biochemical processes allowed the authors to plan the further studies to find some new potential drugs. Thus, the effects of 2-(4-R-5-R'-4H-1,2,4-triazol-3-yl)cyclohexanecarboxylic acids on the induction of phytohemagglutinin-A proliferation of blood mononuclear cells, and the production of cytokines (tumor necrosis factor-α and interleukin-6) on cell culture were studied. The results of the investigations showed that the compound 1.85 has a profound inhibitory effect on the proliferation of peripheral blood mononuclear cells at the concentration of 100 μg/ml (69.8%), and the compound 1.100 causes inhibition of production of tumor necrosis factor-α by 47.3%.

The next direction in studying the biological properties of products of the interaction between 1,4- and 1,5-binucleophiles with cyclic anhydrides of dicarboxylic acids is the evaluation of their herbicidal action. Thus, Barton et al. [24] studied

the herbicidal activity of 2-(5,5-disubstituted-4-oxo-2-imidazolin-2-yl)nicotinic acids and the corresponding 2-(4,4-disubstituted-5-oxo-4,5-dihydro-1H-imidazol-2-yl)quinoline-3-carboxylic acids. The synthesized compounds were tested on models of herbicidal activity on plants both in the embryonic state and after germination. It was found that tested compounds showed pronounced herbicidal activity.

The work [25], which is devoted to the study of the herbicidal activity of 2-(2-imidazolin-2-yl)pyridine-3-carboxylic acid derivatives, can be considered as a continuation of the study, which were mentioned above [24]. The research was carried out on a sample of sixteen single- and dicotyledonous plants. It was shown that the studied compounds caused a cessation of growth or complete destruction of model plants in most cases.

Screening of the combinatorial library of products of the interaction between 1,4-binucleophiles with cyclic anhydrides of dicarboxylic acids for herbicidal activity is described in work [28]. It was found that substituted 2-(4-isopropyl-4-methyl-5-thioxo-4,5-dihydro-1H-imidazol-2-yl)benzoic acids exhibit different levels of herbicidal activity.

It should be noted that the literature contains reports on the use of products of interaction of 1,4- and 1,5-binucleophiles with cyclic anhydrides of dicarboxylic acids in immuno-enzymatic studies. In particular, publication [40] describes the use of the product of cyclocondensation of 4,5,6-triaminopyrimidine with glutaric anhydride (1.136) for the production of monoclonal antibodies. This allows for the immunological determination of N^3-alkylated adenine bases that can be formed as a result of the action of carcino- and mutagenic alkylating exotoxins on DNA.

Based on these calculations and crystallographic studies, the authors conclude that 3-R-8-(3-carboxypropyl)adenine 1.137–1.139 can act as effective haptens of protein molecules, a complex of which can be used to immunize mice to produce appropriate monoclonal antibodies. The results of the studies showed that the complex of protein molecules from 3-methyl-8-(3-carboxypropyl)-adenine (1.137) and 3-n-butyl-8-(3-carboxypropyl)-adenine (1.139) did not give a satisfactory immune response. Instead, the protein conjugates of the compound 1.138 resulted in the production of high affinity monoclonal antibodies. According to the authors, these antibodies can be widely used as an effective eco-monitoring tool, as well as for developing an effective method for monitoring the effectiveness of chemotherapy with anticancer medicines.

Frohner et al. [20] studied the effect of 4-benzimidazolyl-3-arylbutanoic acids on ζ-isoform proteinkinase C (PKCζ). Giving the significant role of this subclass of enzymes in numerical biological processes, it was logical to assume that such protein molecules can be considered as targets for the development of medicinal products. These drugs could potentially be used to correct inflammatory processes that accompany diseases such as asthma, osteoarthritis, psoriasis, sepsis, and others. In addition, this subclass of enzymes is considered as a promising target for the development of new antitumor drugs, which prompted authors to study the inhibitory effects of condensation products of a number of substituted o-phenylenediamine with 3-arylglutaric anhydride on PKCζ.

The investigations were conducted on both cell-free models and cell culture. The work allows identifying a number of highly effective inhibitors of the enzyme mentioned above, in particular 3-(4-chlorophenyl)-4-(5-iodo-1H-benzo[d]imidazol-2-yl)butanoic acid, 3-(3,4-dichlorophenyl)-4-(5-iodo-1H-benzo[d]imidazol-2-yl)butanoic acid and 3-(4-chlorophenyl)-4-(5-phenyl-1H-benzo[d]imidazole-2-yl)butanoic acid. It is these compounds that exhibit an absolute inhibitory effect on PKCζ at the concentration of 200 μmol/L and inhibit its activity by 60–94% at the concentration of 50 μmol/L. On this basis, this work can be a starting point for the creation of a new class of immunomodulatory drugs.

A thorough study [23] reported the biological properties of 3-(1H-benzo[d]imidazol-2-yl)-1,2,2-trimethylcyclopentanecarboxylic acid (1.65) as a condensation product of o-phenylenediamine (1.7) with camphoric anhydride. This compound was tested for antidiabetic, antioxidant activity, as well as for biological safety indicators – acute toxicity and cumulative properties. According to the results of the study of acute toxicity and cumulative properties of compound 1.65, it was found that it is practically non-toxic, weakly cumulative, and in toxic doses, causes a violation of the microstructure of organs that are characteristic of hypoglycemic shock. In the long-term administration in the conditional therapeutic dose does not exert a toxic effect on the organs and systems of experimental animals.

The studies on the presence of antidiabetic properties of 3-(1H-benzo[d]imidazol-2-yl)-1,2,2-trimethylcyclopentanecarboxylic acid (1.65) showed that in single-dose mice with genetically determined and chemically induced non-insulin dependent diabetes mellitus (NIDDM), its hypoglycemic effect

is similar to the analogous effect of the reference compound (glibenclamide). In the model of neonatal-induced streptozotocin NIDDM in the rat, compound 1.65, unlike glibenclamide, prevents diabetic action of chemical factors and the development of absolute and relative insulin deficiency; and it contributes to the restoration of the normal morphological structure of the islet apparatus on the model of dithizone diabetes in rabbits. The long-term (within 30 days) treatment of newborns rabbits with a test compound of 1.65, unlike glibenclamide, does not reduce the nature of the glycemic response during the intraperitoneal glucose tolerance test, does not delay the reversal of glucose intolerance and does not induce pathological changes in the pancreas. It is important that the compound 1.65 shows a higher antioxidant activity in the model of acute toxic hepatitis, by 1.9 times (taking into account the administered doses) than the reference preparation (vitamin E).

Biological activity was established for the products of reaction between cyclic anhydrides of dicarboxylic acids and 3-(2-aminophenyl)-6-R-1,2,4-triazin-5(2H)-ones. Thus, salts of (3-R-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl)-alkylcarboxylic acids were described as promising anti-inflammatory agents [51], 1,2,2-trimethyl-3-(3-methyl-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl)cyclopentane-1-carboxylic acid reveals hypoglycemic activity [52] and phthalimides 1.175 showed moderate anti-tumor activity [49].

Analyzing the results of this work, it can be considered its informative theoretical basis for the creation of new biologically active compounds and drugs for the treatment of non-insulin dependent diabetes mellitus and its vascular complications.

Thus, the analysis of literature data shows that the heterocyclic reaction on the basis of the interaction of 1,4- and 1,5-binucleophiles with cyclic anhydrides of dicarboxylic acids has a number of features of the course, which are determined both by the structure of the starting compounds and the conditions of reaction. The products of the interaction of 1,4- and 1,5-binucleophiles with cyclic anhydrides of dicarboxylic acids exhibit diverse biological activity and may be interesting for the search and creation on their basis of new highly effective and low-toxic medicines.

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РЕАКЦІЇ 1,4-NCCN-, 1,4-NNCN- І 1,5-NCCCN-БІНУКЛЕОФІЛІВ З ЦИКЛІЧНИМИ АНГІДРИДАМИ ДИКАРБОНОВИХ КИСЛОТ ЯК МЕТОД СИНТЕЗУ ГЕТЕРОЦИКЛІЧНИХ СПОЛУК (ОГЛЯД ЛІТЕРАТУРИ)

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В огляді наведено критичний аналіз літературних даних щодо особливостей реакції 1,4-NCCN-, 1,4-NNCN і 1,5-NCCCN-бінуклеофілів з циклічними ангідридами дикарбонових кислот. Показано, що реакція названих ангідридів з 1,4-NCCN-бінуклеофілами приводить до утворення імідазольного фрагменту з карбоксилвмісним залишком. Показано, що бензімідазоли є одними з найбільш досліджених продуктів реакції 1,4-NCCN-бінуклеофілів з циклічними ангідридами карбонових кислот, що пов'язано з доступністю вихідних сполук. Також обговорено підходи до хімічної модифікації зазначених продуктів. Встановлено, що 1,4-NNCN-бінуклеофіли, які використовуються в реакціях з циклічними ангідридами дикарбонових кислот, надані переважно амідинами та амідразонами. Описано вплив структур вихідних сполук та умов реакцій на будову її продуктів. Відповідно до літературних даних реакція 1,5-NCCCN-бінуклеофілів, таких як аміди та гідразиди антранілової кислоти, діамінозаміщені поліциклічні арени та 2-азагетериланіліни з циклічними ангідридами дикарбонових кислот, зазвичай приводить до утворення похідних піримідину. Показано, що застосування як реагентів циклічних ангідридів несиметричних дикарбонових кислот може обумовити неоднозначність перебігу реакції. У той же час, формування одного продукту взаємодії бінуклеофілів з несиметричними ангідридами може бути досягнене варіюванням умов реакції. Детально розглянуто біологічну активність розглянутих продуктів реакції. Показано, що зазначені сполуки проявляють антибактеріальну, протигрибкову, протиракову, імуномоделюючу та гіпоглікемічну активності.

Ключові слова: бінуклеофіли, циклічні ангідриди дикарбонових кислот, аміни, гідразини, 2-азагетериланіліни, гетероцикли, біологічна активність.

REACTIONS OF 1,4-NCCN-, 1,4-NNCN- AND 1,5-NCCCN-BINUCLEOPHILES WITH DICARBOXYLIC ACIDS CYCLIC ANHYDRIDES AS A METHOD OF HETEROCYCLIC COMPOUNDS SYNTHESIS (A REVIEW)

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Critical analysis of published information related to the features of reaction of 1,4-NCCN-, 1,4-NNCN and 1,5-NCCCN-binucleophiles with cyclic anhydrides of dicarboxylic acids has been presented in the review. It has been shown that the reaction of named anhydrides with 1,4-NCCN-binucleophiles leads to the formation of the imidazole fragment that contains carboxyl-containing moiety. It has been shown that benzimidazole derivatives are among the most studied products of reaction between 1,4-NCCN- and cyclic anhydrides of dicarboxylic acids due to the high availability of initial compounds. The approaches to chemical modification of latter compounds have been discussed as well. It has been found out that 1,4-NNCN-binucleophiles used in reactions with cyclic anhydrides of dicarboxylic acids are mostly presented by amidines and amidrazones. The effects of structures of initial compounds and conditions of reactions on the products of reaction have been described. Literature data shows that the reaction of 1,5-NCCCN-binucleophiles such as amides and hydrazides of anthranilic acid, diamino-substituted polycyclic arenes and 2-azaheterylanilines with cyclic anhydrides of dicarboxylic acids commonly results in the formation of pyrimidine derivatives. It has been established that the application of cyclic anhydrides of non-symmetric dicarboxylic acid as reagents may cause the ambiguity of the reaction pathways. However, the formation of single products of interaction between binucleophiles and non-symmetric anhydrides can be achieved by variation of reaction conditions. The biological activity of the discussed reaction products has been considered in detail. It has been shown that the above-mentioned compounds reveal antibacterial, antifungal, anticancer, immunomodulate, and antidiabetic activities.

Keywords: binucleophile; cyclic anhydride of dicarboxylic acid; amine; hydrazine; 2-azaheterylaniline; heterocycle; biological activity.

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