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TRIAZOLO- AND TETRAZOLOISOINDOLES. (REVIEW)

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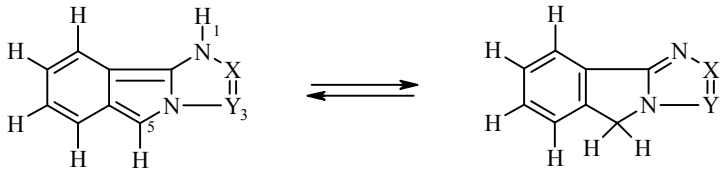
Data on methods for the synthesis of derivatives of triazolo- and tetrazoloisoindoles and their chemical characteristics are reviewed. The data from quantum-chemical calculations of some structures are presented. Possible practical applications of the compounds are indicated.

Keywords: tetrazoloisoindoles, triazoloisoindoles, cyanine dyes, biological activity, synthesis methods, chemical characteristics, electronic structure.

Isoindole chemistry has approximately a third of the age of indole chemistry [1]. In spite of this, however, the simplest isoindoles have now been studied quite extensively [2, 3]. On the other hand, condensed isoindoles have not been investigated systematically; there are a large number of papers on the synthesis of their derivatives and patents in which their characteristics of practical significance are described, but these data have not yet been appraised except in the case of fairly brief and early (1961) reviews on specific systems [4]. In the present review we examine data on methods of synthesis, chemical transformations, and also biological and other useful characteristics of triazolo- and tetrazoloisoindole derivatives, published before September, 2001.

Since compounds with the aromatic system of the isoindole fragment belonging to these groups (e.g., of type **A**) are extremely unstable, their significantly more stable 5-H tautomers (e.g., of type **B**) have mainly been described in the literature.



A **B**

X = N, Y = CH or X = CH, Y = N; X = Y = N

1. METHODS OF SYNTHESIS

1.1. 1,2,4-Triazolo(5,1-*a*)isoindoles

The first representative of triazoloisoindole systems of type **A**, i.e., 1-methyl-2-phenyl-1,2,4-triazolo[5,1-*a*]isoindole (**1**), was obtained by the action of a 10% aqueous solution of sodium hydroxide on the salt **2** (for the preparation of the salt, see section 3.2) [5,6]. The aromatic characteristics of compound **1** are

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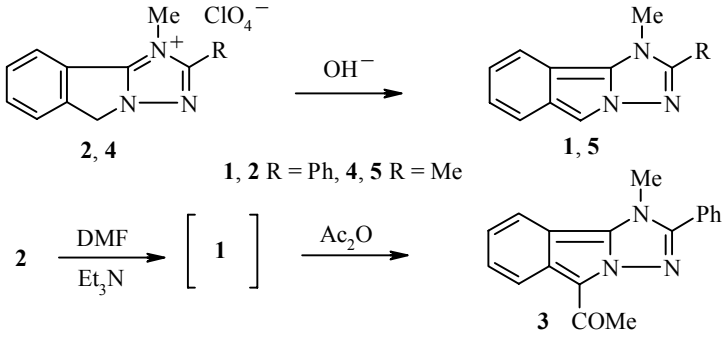
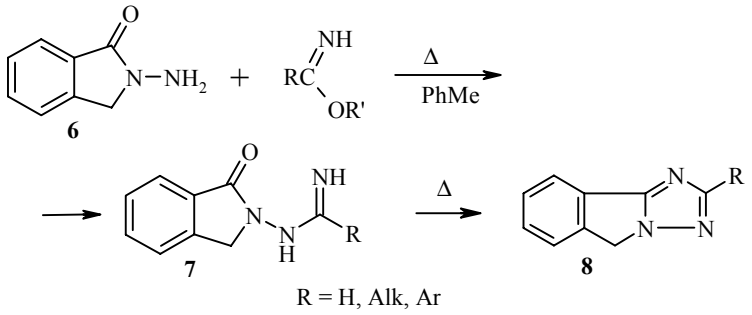
indicated by features of its ^{1}H NMR spectrum and also by its ability to enter into electrophilic substitution. For example, the action of acetic anhydride on the triazoloisoindole **1** at position 5 leads to the acetyl derivative **3** [5, 6], and this agrees with the calculations [7].



The even more unstable dimethyl derivative **5**, which decomposes in air in 5 min, was obtained from the salt **4** by the action of potassium hydroxide [7]. Its UV spectrum agrees well with the calculated data [7]. Recently* it has been possible to record the ^{1}H NMR spectrum of this substance in deuteroacetone, δ, ppm (*J*, Hz): 2.55 (3H, s, C–CH_3); 3.95 (3H, s, N–CH_3); 6.68 (1H, td, ^3J = 7.5 and ^4J = 1.5, 8-H); 6.90 (1H, td, ^3J = 7.5 and ^4J = 1.5, 7-H); 7.30 (1H, s, 5-H); 7.45 (1H, d, ^3J = 7.5, 9-H); 7.75 (1H, d, ^3J = 7.5, 6-H).

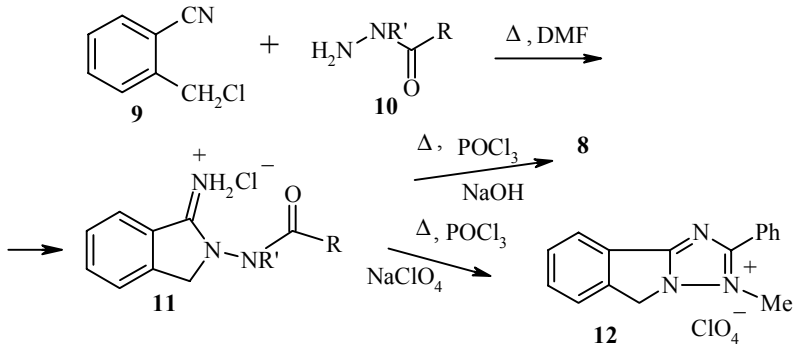
Among known methods for the production of derivatives of 1,2,4-triazolo[5,1-*a*]isoindole of type **B** it is possible to single out two methods of the same type.

The first is based on the fact that the reaction of N-aminophthalimidine (**6**) with imidic esters under the conditions for the formation of amidines leads to compounds **7**, which undergo cyclization when heated into 2R-5H-1,2,4-triazolo[5,1-*a*]isoindoles **8**. Twenty five compounds of type **8** were synthesized by this method (yields from 39%, R = 2-MeC_6H_4, to 77%, R = Ph) [8].



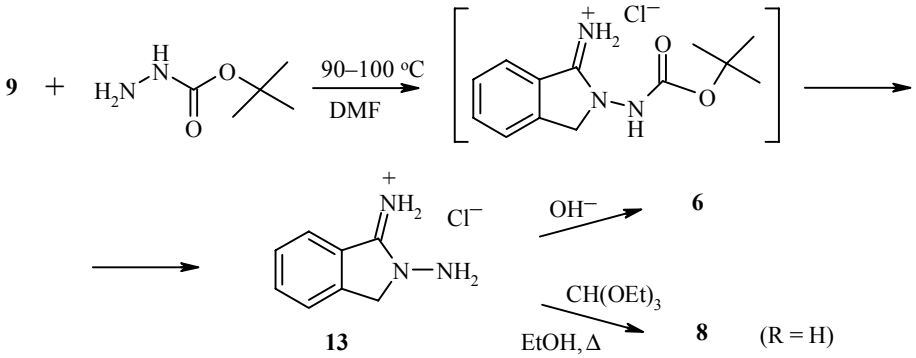
The second method involves the formation of salts **11** from the *o*-chloromethylbenzonitrile (**9**) and carboxylic acid hydrazides **10** (R' = H). Cyclization of the products by heating in phosphorus oxychloride followed by treatment with 5% aqueous sodium hydroxide (R' = H) leads to the products **8** (yields from 17%, R = C_5H_{11}, to 98%, R = C_6H_5) [9, 10]. Subsequent treatment with sodium perchlorate (R = Ph, R' = Me) leads to the salt **12** (yield 67%) [6].

* Unpublished data of the authors of the present review.

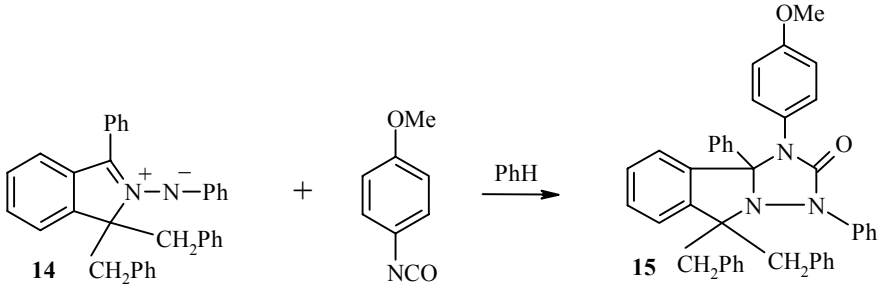


R = Me, Et, C_5H_{11}, Ph, 4-$O_2NC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, 1-naphthyl, 2-furyl, 2-thienyl

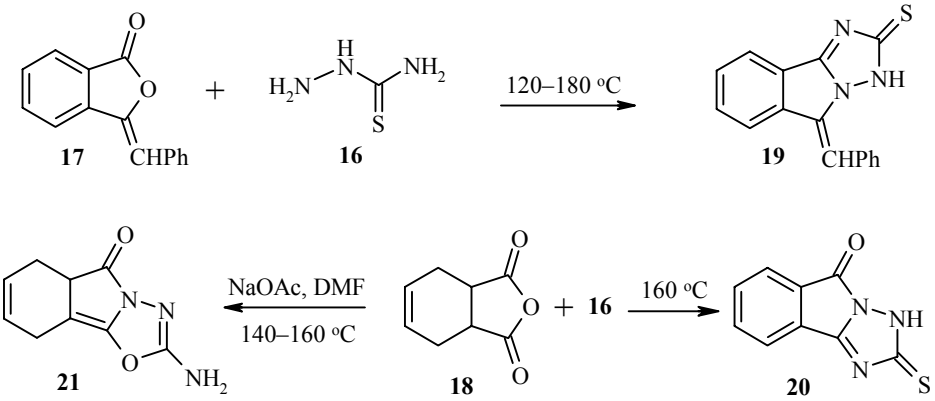
Compound **8** with R = H could not be synthesized in this way on account of the ease of self-condensation of the initial formylhydrazine. However, it was obtained with a yield of 32% by the reaction of the nitrile **9** with *tert*-butoxycarbonylhydrazine followed by treatment of the obtained salt **13** with orthoformic ester. Alkaline hydrolysis of the salt **13** led to N-aminophthalimidine (**6**) [11, 12].



When heated cautiously to 60-70°C, the stable azomethine imine **14** produced by irradiation of 1,1-dibenzyl-2,4-diphenyl-1,2-dihydrophthalazine (quartz lamp, benzene–diethylamine, 1:1) enters into 1,3-dipolar cycloaddition with *p*-methoxyphenyl isocyanate, being converted with high yield (94%) into the triazoloisoindole **15** [13].

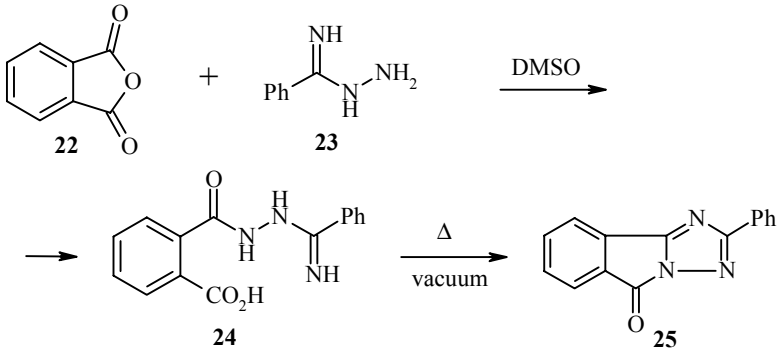


The reaction of thiosemicarbazide (**16**) with benzylidenephthalide **17** or tetrahydrophthalic anhydride **18** gave the derivatives **19** (yield 69%), **20** (49%), or **21** (58%).

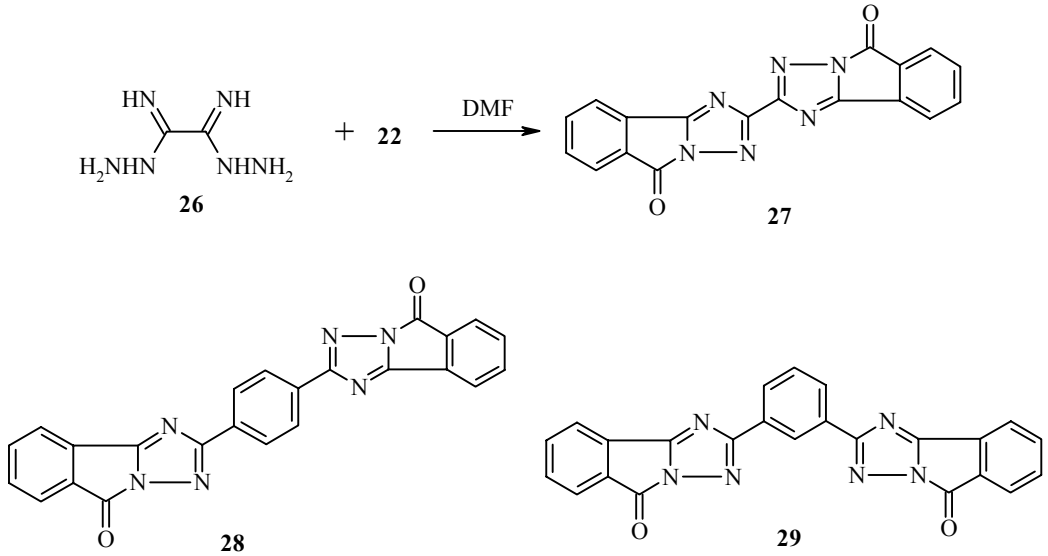


It should be noted that differing products (**20** or **21**) are formed in the case of tetrahydrophthalic anhydride, depending on the reaction conditions (see the scheme) [14].

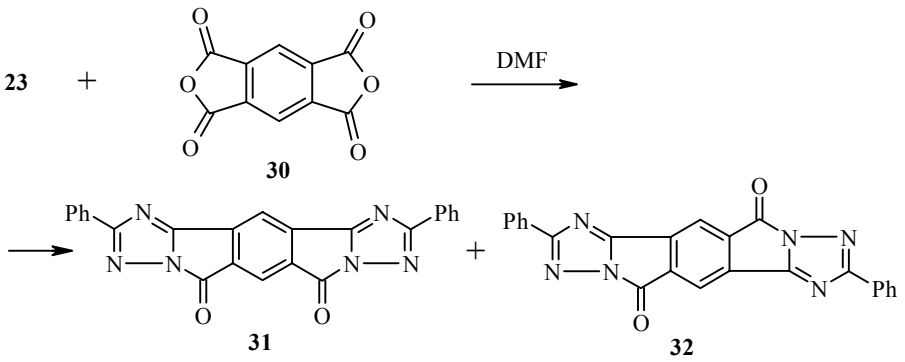
The acylation product **24** is formed during the condensation of equimolar amounts of phthalic anhydride (**22**) with benzohydrazide imide (**23**) [15]. The action of heat on the product under vacuum leads to 2-phenyl-5H-1,2,4-triazolo[5,1-*a*]isoindol-5-one (**25**) (yield 53%) [15, 16].



The reaction takes place similarly with oxalohydrazide diimide **26**, and the bistriazoloisoindoledione **27** is formed (yield 50%). The *p*- and *m*-phenylenebistriazoloisoindolones **28** (yield 54%) and **29** (yield 52%) are formed from terephthalohydrazide and isophthalohydrazide diimides [17].

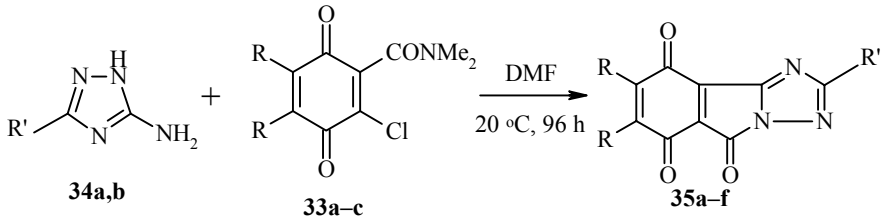


A mixture of the *cis* and *trans* products **31** and **32** was obtained from benzohydrazide imide **23** and pyromellitic dianhydride **30** respectively [15, 18].



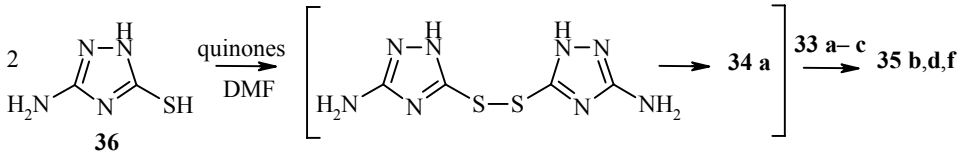
The reactions of dianhydrides **30** with bisamidrazones lead to high-molecular compounds with the so-called staircase structure. The bisamidrazones of terephthalic, isophthalic [17, 19, 20], oxalic [19, 20], and pyridine-2,6-dicarboxylic [21] acids, on the one hand, and the anhydrides of pyromellitic [19-21], 3,3',4,4'-diphenyloxy-, 3,3',4,4'-benzophenone-, and 3,3',4,4'-diphenylsulfonetetracarboxylic acids [19-21], on the other, were submitted to polycondensation.

The reaction of benzo- and naphthoquinone derivatives **33a-c** (obtained from the corresponding 1,2-dichloro-substituted compounds and DMF) with the amino and diamino derivatives of 1,2,4-triazole **34a**,**b** in DMF gave 62-74% yields of the 1,2,4-triazolo[5,1-*a*]isoindolinetrione derivatives **35a-f** [22].

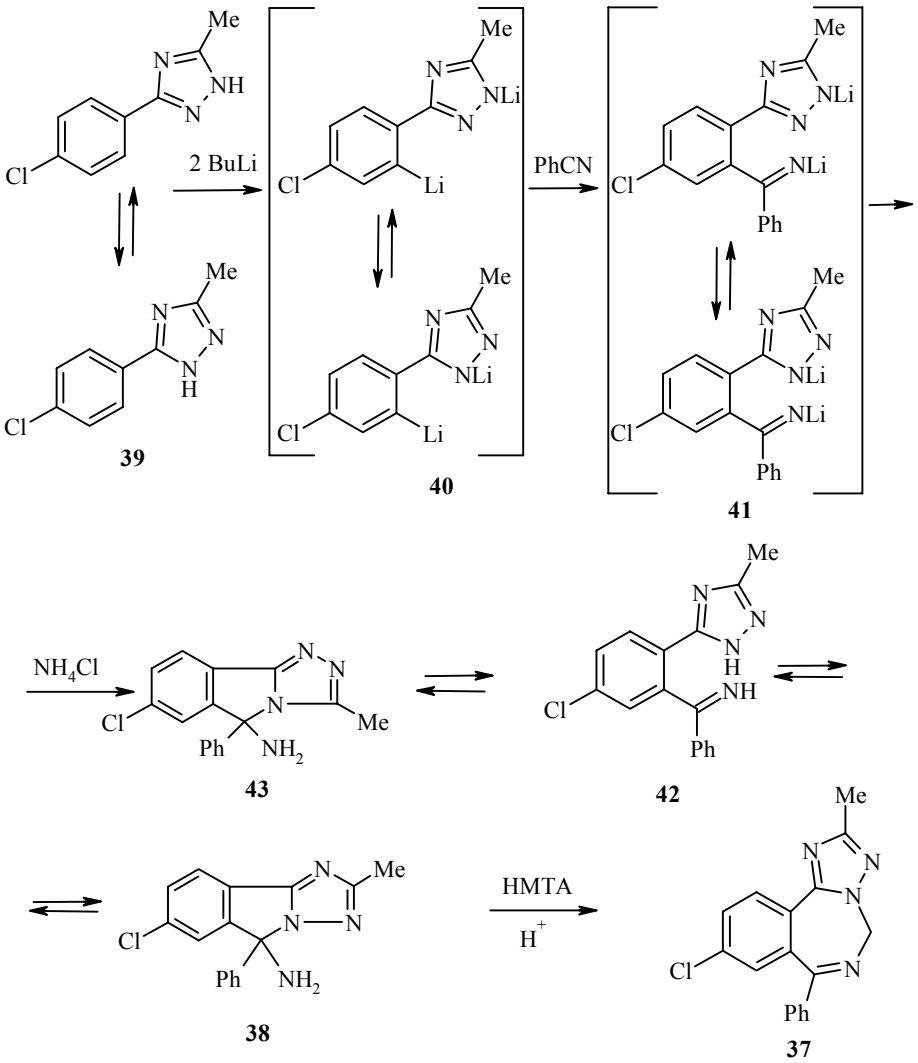


33 a R = Cl, **b** R = CN, **c** R+R = CH=CHCH=CH; **34 a** R' = H, **b** R' = NH_2;
35 a, **b** R = Cl, **c**, **d** R = CN, **e, f** R+R = CH=CHCH=CH; **a**, **c**, **e** R' = H **b**, **d**, **f** R' = NH_2

Compounds **35b**,**d**,**f** were synthesized with yields of 64-74% by the reaction of **33a-c** with the aminomercapto derivative **36** [22]. In the opinion of the authors [22] the intermediate disulfide is transformed under the reaction conditions into the aminotriazole **34a**. The structure of the products **35a-f** was confirmed by the IR and mass spectra and also by the ^{1}H NMR spectra [22].



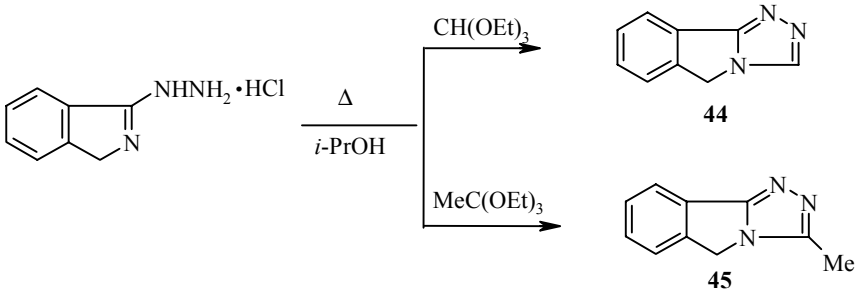
The triazolobenzodiazepine **38**, obtained according to the scheme below, was used as starting compound for the synthesis of triazolobenzodiazepine **37**, which is an isomer of the psychopharmacological product alprozolam [23-25]:



The transformation **39** → **38** takes place in the cold and in an inert atmosphere with a yield of 50% [25]. It should be noted that the action of such a strong base as butyllithium does not affect the chlorine atom at the *para* position of the benzene ring in the aryltriazoles **40** and **41**. The structure of the product **38** was not rigorously established. The main arguments in favor of such a structure are the presence, proved by the ^{1}H NMR spectra, of the open form **42** in the solution and the rule for condensed 1,2,4-triazoles according to which the [5,1-*a*] isomer (i.e., compound **38**) is thermodynamically more stable than the [3,4-*a*] isomer (i.e., compound **43**). The triazoloisoindole **38** is transformed into compound **37** by the action of hexamethylenetetramine (HMTA) in the presence of a strong acid. This can be regarded as a variant of the intramolecular Mannich reaction [25].

1.2. 1,2,4-Triazolo[3,4-*a*]isoindoles

There is very little information on the synthesis of compounds of the 1,2,4-triazolo[3,4-*a*]isoindole series. Familiar examples are based on the use of 1-hydrazoindolenine derivatives. Thus, condensation of the perchlorate with triethyl orthoformate and orthoacetate gave the simplest member of the group **44** (yield 48%) and its 3-methyl-substituted derivative **45** (yield 46%) respectively [26].

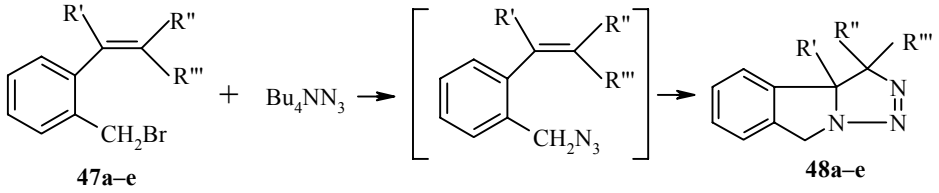


The triazoloisoindole derivatives were not obtained if the ortho esters were replaced by carboxylic anhydrides, chlorides, or esters [26].

When the acetyl derivative **46** was heated with polyphosphoric acid, compound **45** was isolated from the reaction products with a yield of 42% [27].

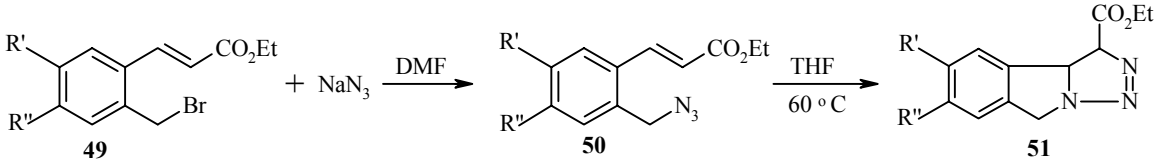
1.3. *vic*-Triazoloisoindoles

There are no examples of the synthesis of *vic*-triazoloisoindole and its derivatives in the literature. Only methods for the synthesis of certain partially hydrogenated derivatives have been described. For instance, intramolecular dipolar cycloaddition was used for the synthesis of compounds of the *vic*-dihydrotriazoloisoindole series. Thus, the reaction of the bromides **47a-e** with tetrabutylammonium azide leads to the formation of the triazoloisoindoles **48a-e**. Here only compounds **48a**,**d**,**e** were isolated in the individual state with yields in the order of 78% [28].



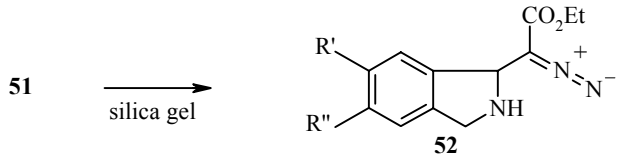
47, 48 a–c R' = H, **d, e** R' = Me; **a** R" = COOMe, **b–e** R" = CN; **a**, **b**, **d** R''' = COOMe, **c, e** R''' = CN

Dihydrotriazoloisoindoles **51** were obtained with yields of 8-20% by reaction of the bromides **49** with sodium azide through the intermediate azides **50**, and compounds **50** were also isolated and characterized [29].

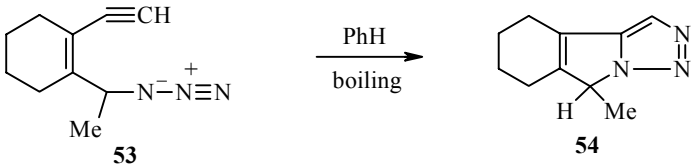


49–51 a–c R' = H, **d** R' = OCH_2O, **a** R" = H, **b** R" = OMe, **c** R" = Cl, **d** R" = OCH_2O

The structure of the products **51**, purified by chromatography on silica gel, was confirmed by the IR and mass spectra and also by the ^{1}H NMR spectra. The low yields of these compounds are explained by isomerization to compounds of type **52** during purification.

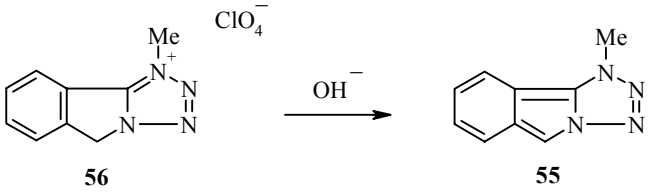


When a benzene solution of the azide **53** was boiled, the tetrahydro derivative of triazoloisoindole **54** was obtained (yield 90%) [30-31]. In [31] this compound was isolated in the pure form by chromatography on silica gel (yield 92%). Its composition and structure were confirmed by elemental analysis and IR and ^{1}H NMR spectra.



1.4. Tetrazoloisoindoles

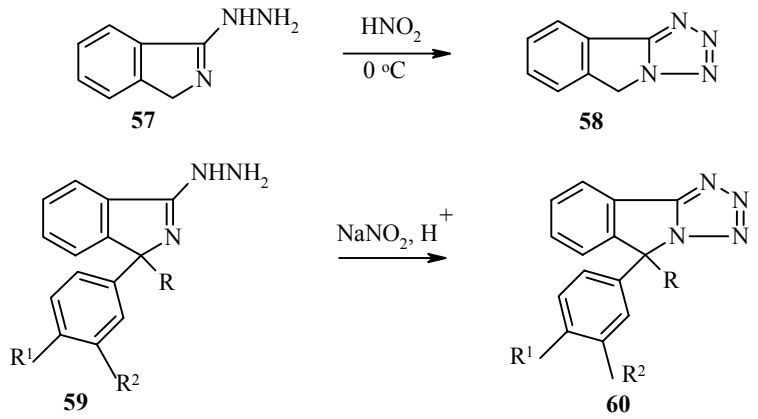
Like 1,2,4-triazoloisoindole of type **A** (see section 1.1) its analog with a tetrazole ring **55** was obtained by the action of a 5% aqueous solution of sodium hydroxide on the salt **56** (for the production of the salt, see section 3.2).



When treated with acid compound **55** is converted into the initial salt, and when stored in air it soon decomposes [32]. Its aromatic characteristics are confirmed by the ^{1}H NMR spectra and by the ability to enter into electrophilic substitution (see section 3.1).

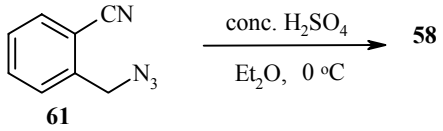
The usual method of adding the tetrazole ring to the isoindole system in order to produce tetrazoloisoindole derivatives of type **B** involves treatment of the corresponding hydrazinoindolenine with nitrous acid.

Thus, 5H-tetrazolo[5,1-*a*]isoindole (**58**) (yield 70%) was obtained from 1-hydrazinoindolenine (**57**) [33], while the corresponding disubstituted 5H-tetrazoloisoindoles **60** were obtained from its 3,3-disubstituted derivatives **59** [34-36].

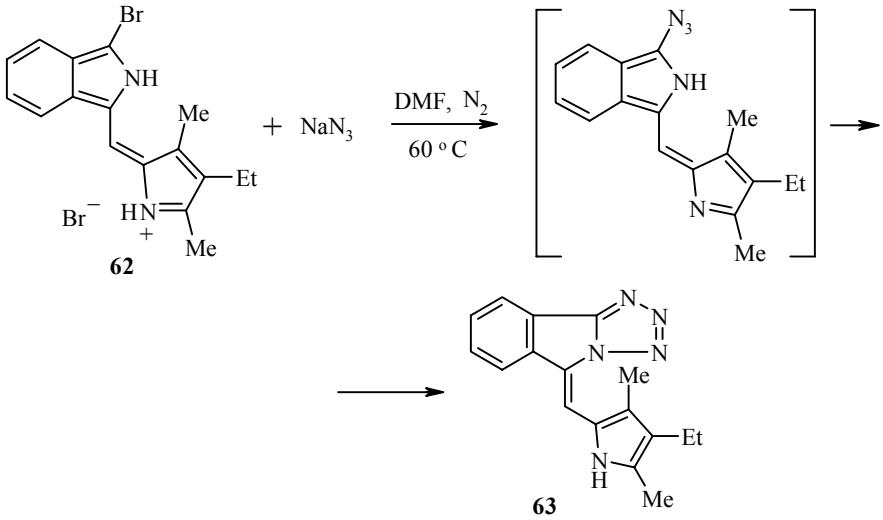


R = Me, *i*-Pr, CH_2Ph, $CH_2{=}CHCH_2$, $CH_2C{\equiv}CH$; R^1 = Cl, MeO; R^2 = H, Cl, MeO,

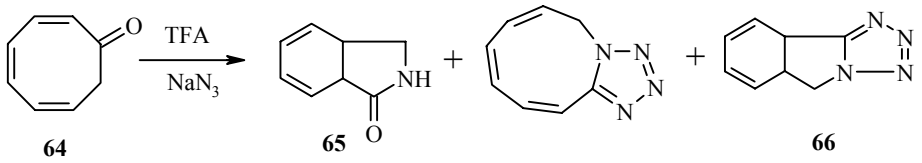
When treated with concentrated sulfuric acid in the cold *o*-azidomethylbenzonitrile (**61**) is converted fully into 5H-tetrazoloisoindole (**58**). If the cooling is insufficient, vigorous decomposition of the azide occurs [32].



During reaction of 1-bromo-8-ethyl-7,9-dimethylbenzopyrromethene hydrobromide (**62**) with sodium azide in DMF in an atmosphere of nitrogen 8-ethyl-7,9-dimethyltetrazolo[1,5-*i*]benzopyrromethene (**63**) was obtained with a yield of 47%. Its composition and structure were confirmed by X-ray crystallographic analysis, elemental analysis, the IR, UV, and mass spectra, and the ^{1}H NMR spectra [37].



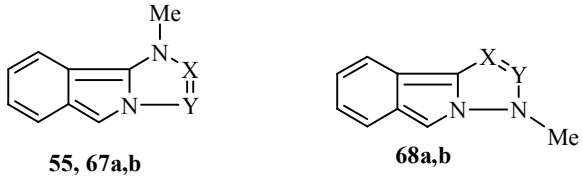
The Schmidt reaction with the ketone **64** in concentrated hydrochloric acid or sulfuric acid only gives 3,7a-dihydrophthalimidine (**65**). In trifluoroacetic acid three products are formed, including 5a,9a-dihydro-5H-tetrazolo[5,1-*a*]isoindole (**66**) (yield 6.5%) [38].



64 **65** **66**

2. THEORETICAL ASPECTS

The structure of N-methyl-substituted triazolo- and tetrazoloisoindoles **67a**,**b**, **55** and **68a**,**b** was calculated by the PPP and CNDO/2 methods respectively [7].



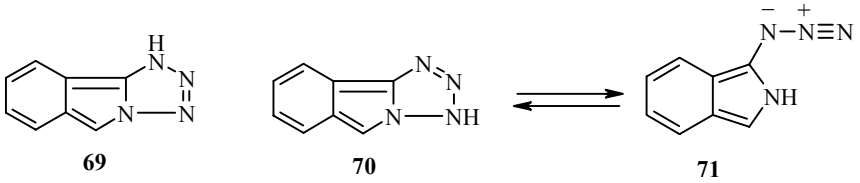
55, 67a,b **68a,b**

55 X = Y = N; 67 a X = N, Y = CH, **b** X = CH, Y = N; **68 a** X = N, Y = CH, **b** X = Y = N

It was concluded on the basis of analysis of the canonical and localized MOs that the compounds can be regarded to a first approximation as 1,2-disubstituted isoindoles, i.e., 10π-electron systems and not 14π-electron systems, as would be expected on the basis of the structural formulas. In this they differ substantially from the azinoisoindoles [39], which are 14π-electron systems. It was established that the stronger internuclear conjugation in the tricyclic system leads to greater stability. This may be why the azoloisoindoles are much less stable systems than azinoisoindoles. The degree of conjugation in the azoloisoindoles through the nitrogen atoms of pyrrole type depends on their position. Comparison of the π-energies and the general electronic energies of the isomeric structures of compounds **55**, **67**, and **68** shows that the compounds **67b** and **55** must be the most stable. To judge from the values of the HOMO energies, calculated by the PPP method, it can be supposed according to Koopmans theorem that the ionization potentials increase in the order: **68a** < **67b** < **67a** < **55** < **68b**. The investigated compounds can be arranged in the same order according to the degree of stability to oxidation. A different order is obtained for triazoloisoindoles during comparison of the HOMO energies calculated by the PPP/2 method: **67a** < **67b** = **68a** < **55** < **68b**. According to the values of the charges on the atoms, the most probable points of electrophilic attack in triazolo- and tetrazoloisoindoles are the α position of the pyrrole ring and then the pyridine-type nitrogen atom in the neighboring azole ring. Comparison of the charges on the atoms of the benzene and tri- or tetrazole rings shows that the latter must be more reactive toward nucleophilic reagents. In the first singlet excited state of all the investigated structures the bonds are equalized and the internuclear conjugation is stronger [7].

On the basis of calculated data on the electronic structure of compounds **67a**,**b**, **55**, and **68a**,**b** it was suggested that they may participate in the Diels–Alder reaction, and their comparative activity in this process was assessed. From the set of characteristics as a whole it is possible to propose high diene activity for the tri- and tetrazoloisoindoles, close to that of the parent isoindole. The most active in the diene synthesis must be compounds **67b**, **55**, and the least active must be compound **68b** [40] (see also section 3.4).

The obtained calculated data agree well with the known chemical characteristics and UV spectra of the triazolo- and tetrazoloisoindole derivatives [5-7, 32, 41-42].



69 **70** **71**

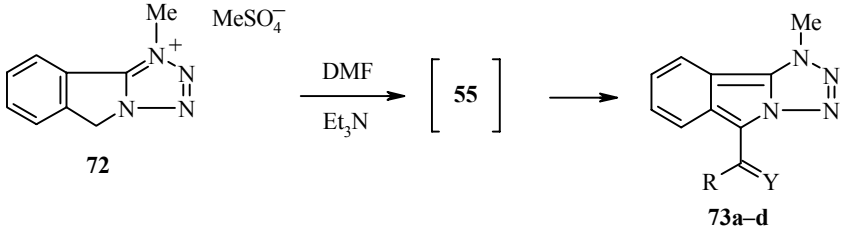
Energies of the π systems equal to 24.60 (21.42) β, 21.70 (20.60) β, and 20.46 (20.42) β respectively were calculated for 1H- and 3H-tetrazole[5,1-*a*]isoindoles **69** and **70** and also for the possible open form **71** in the supposed azidotetrazole tautomerism **69-71** by the HMO method with the topological parameters supplemented according to the REGMUL software and by the simple HMO method (in parentheses). On the basis of comparison of these energies it was suggested that azidotetrazole tautomerism may occur [43]. Its existence in the tetrazoloisoindole series was confirmed experimentally for the case of compound **63** [37].

3. CHEMICAL CHARACTERISTICS

3.1. C-Acylation

As already mentioned above (see sections 1.1 and 1.4), isoindoles of type **A** with the aromatic system of the isoindole fragment are capable of entering into electrophilic substitution. This was demonstrated for the case of the transformation of triazoloisoindole **1** into the 5-acetyl derivative **3** during treatment with acetic anhydride (see section 1.1).

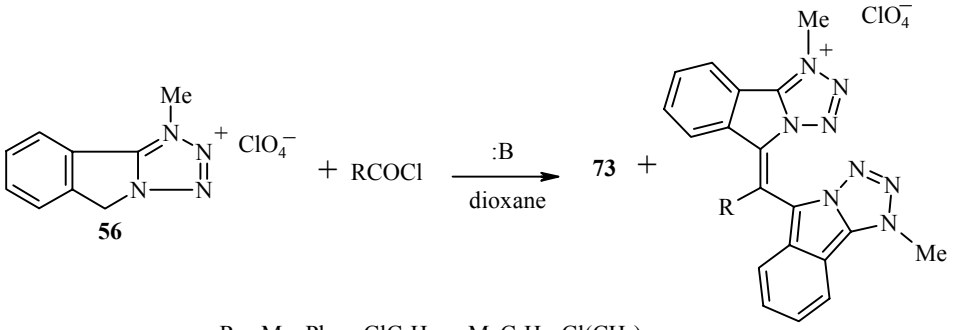
The tetrazoloisoindole **55**, obtained from the salt **72** without isolation (for the production of the salt, see section 3.2), forms the derivatives **73a**,**b** (yields 88 and 72% respectively) with acetic and benzoic anhydrides and the addition products **73c**,**d** (yields 80 and 66% respectively) with isocyanates and isothiocyanates. Unlike the initial compound **55**, all substances of type **73** are fully stable during storage [44].



72 **73a–d**

a–c Y = O, **a** R = Me, **b** R = Ph, **c** R = NHC_6H_4Me-*p*; **d** Y = S, R = NHPh

Recently it was found that during the acylation of the salt **56** by carboxylic acid chlorides cyanine dyes with general formula **74** are also formed with yields in the order of 40% in addition to the expected acyl derivatives of type **73** (Y = O) [45, 46]. Thus, a new method was proposed for the synthesis of cyanine dyes of the tetrazoloisoindole series, making it possible to vary R within wide limits.



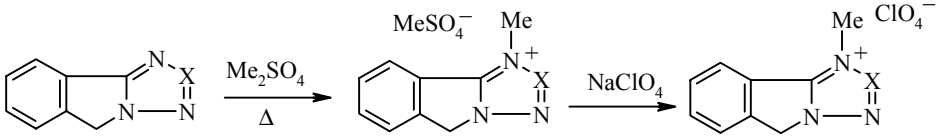
56

R = Me, Ph, *o*-ClC_6H_4, *p*-MeC_6H_4, $Cl(CH_2)_3$

74

3.2. N-Alkylation

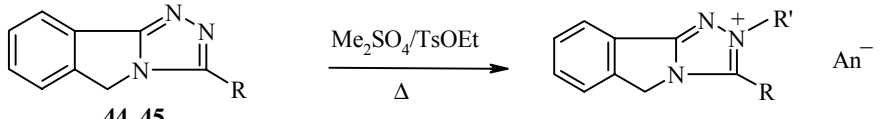
The results from alkylation of the triazoloisoindoles **8** (R = Ph), **44** and **45** [26], and also tetrazoloisoindole **58** [32] indicate that this reaction takes place at a specific position of the tetrazole ring, depending on the structure of the initial azole. Thus, compounds **8** and **58** are methylated at position 1 with the formation of the salts **75** (yield 96%) and **72** (yield 80%) respectively. The structure of the salt **75** was proved by comparing the perchlorate **2** obtained from it with the isomeric perchlorate **12** (for the synthesis, see section 1.2) [6]. The structure of the methyl sulfate **72** and of the perchlorate **56** obtained from it was established on the basis of the chemical transformations: Reduction of the salt **72** with zinc dust in dilute hydrochloric acid gave the hydrochloride of 1-methyliminoisoindoline in the form of a complex with zinc chloride. Treatment of this complex with sodium sulfite followed by extraction with chloroform and the action of perchloric acid on the extract gave 1-methyliminoisoindoline hydrochloride, alkaline hydrolysis of which led to phthalimide and methylamine [32].



8, 58 **72, 75** **2, 56**

2, 8, 75 X = CPh; **56, 58, 72** X = N

Quaternization of compounds **44** and **45** with dimethyl sulfate or ethyl tosylate takes place at the nitrogen atom at position 2 with the formation of the products **76**, and this is confirmed by quantum-chemical calculations [26].



44, 45 **76**

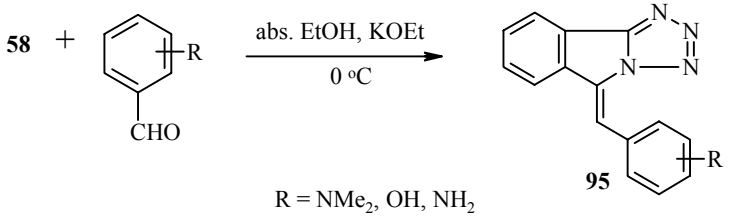
R = H, Me; R' = Me, Et; An = $MeSO_4$, TsO

3.3. Reactions at the Active Methylene Group

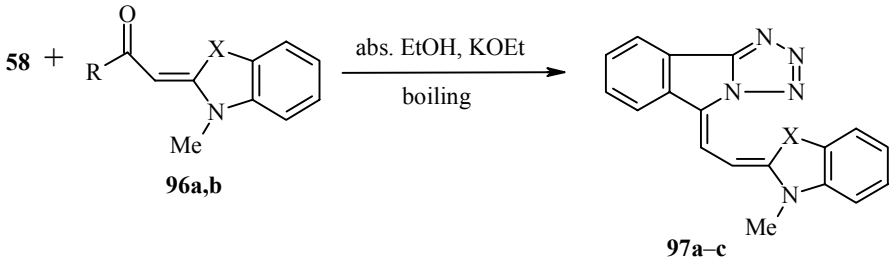
The salts **2** and **12** and also the free base **8** (R = Ph) are capable of acting as methylene component in reaction with carbonyl compounds, leading to the formation of the dyes **77-85** [6, 41] (see Table 1 [6]).

It was shown that 2-methyltetrazole **55** and its salts are also active in the reaction [41, 42, 44]. The dyes **86-94** were obtained from these compounds (Table 2 [42]).

Like compound **8** (R = Ph), the tetrazoloisoindole **58** can enter into condensation with carbonyl compounds, e.g., with aldehydes, resulting in the formation of a series of products **95** with yields of 60-95% [44].



Analogous condensation can be realized with the N-alkyl-2-formylmethylene derivatives of nitrogen heterocycles **96a** or with their N-alkyl-2-acetanilidovinyl derivatives **96b**, and the colored substances **97a** (yield 98%), **97b** (62%), and **97c** (70%) are obtained [44].



96 X = CMe_2, S, CH=CH; **a** R = H, **b** R = NHPh; **97 a** X = CMe_2, **b** X = S, **c** X = CH=CH

Unlike compounds **2**, **12**, and **56**, quaternary salts of type **76** do not enter into similar condensations. On the other hand, 5H-1,2,4-triazolo[3,4-*a*]isoindole perchlorate (**98**) reacts with 1-methyl-2-formylmethylene-1,2-dihydroquinoline in the presence of acetic anhydride with the formation of the dye **99**.

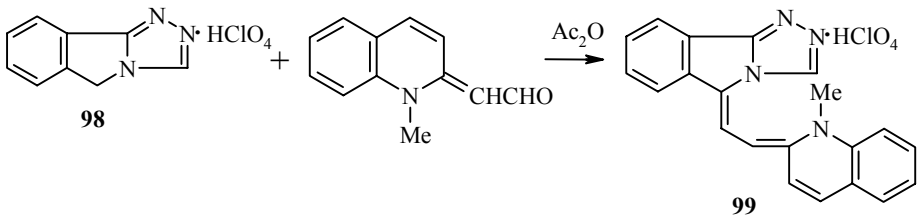
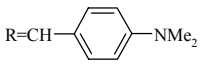
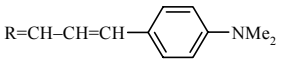
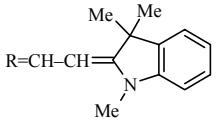
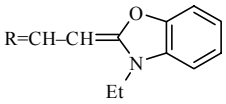
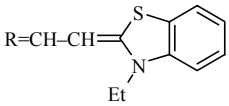
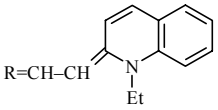
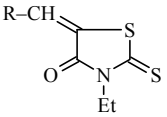
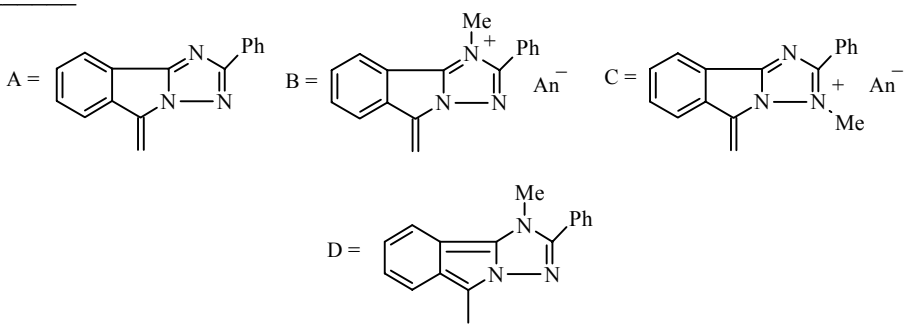


TABLE 1. The Physical Characteristics of Dyes of the Triazoloisoindole Series

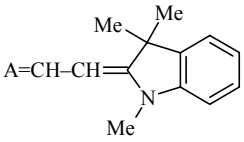
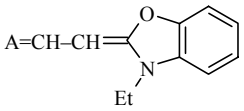
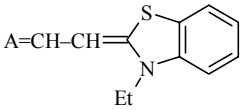
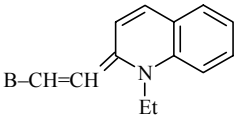
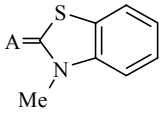
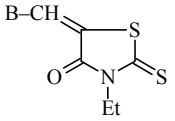
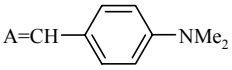
Compound	General formula	R*	An^-	UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-4}$), in methanol	Yield, %
77a		A	—		
77b		B	ClO_4		
77c		C	ClO_4		
78a		A	—	465 (4.10)	60
78c		C	ClO_4	528 (6.25)	56
79a		A	—	484 (5.60)	96
79b		B	ClO_4	526 (8.00)	37
79c		C	ClO_4	534 (7.13)	80
80a		B	I	512 (10.00)	68
80b		C	ClO_4	517 (10.13)	85
81a		A	—	510 (6.90)	76
81b		B	I	550 (7.38)	53
81c		C	ClO_4	552 (11.25)	51
82		B	I	603 (6.38)	57
83		D		544 (4.94)	81
84	B=CH–R	D	ClO_4	568 (3.88)	69
85	B=CH–CH=CH–R	D	ClO_4	672	56

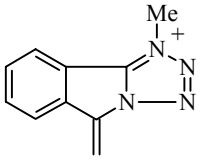
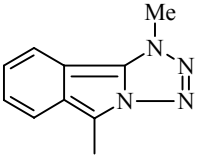
*

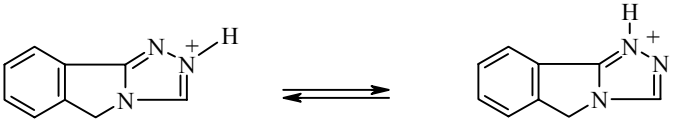


This difference in the behavior of the quaternary and simple salts is explained by the ability of the proton to migrate from the nitrogen at position 2 to position 1 during condensation. Of structures **100** and **101** only in the latter is the methylene group at position 5 conjugated with the positively charged nitrogen atom and active in cyanine condensations. Analogous migration of the substituent R' is of course impossible in quaternary salts of type **76** [26].

TABLE 2. The Physical Characteristics of Dyes of the Tetrazoloisoindole Series

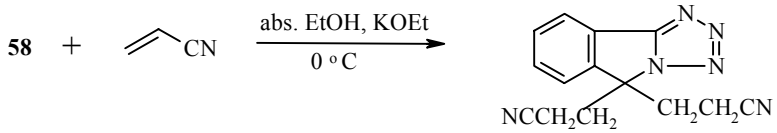
Compound	General formula*	An^-	UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-4}$) (solvent not indicated)	Yield, %
86	A=CH–B	ClO_4	557 (7/2)	85
87	A=CH–CH=CH–B	ClO_4	651 (7.7)	91
88		ClO_4	539 (16.2)	92
89		I	516 (3.5)	85
90		ClO_4	555 (7.4)	69
91		—	580 (8.9)	85
92		ClO_4	448 (2.2)	70
93		—	539 (5.1)	54
94		ClO_4	521 (3.8)	89

* A =  An^- B = 



100 **101**

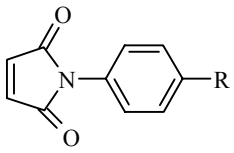
In addition to the reactions involving the CH_2 and C=O groups discussed above the cyanoethylation of compound **58** with acrylonitrile has also been described. It takes place in an alkaline medium and leads to the disubstituted product **102** with a yield of 73% [44].



102

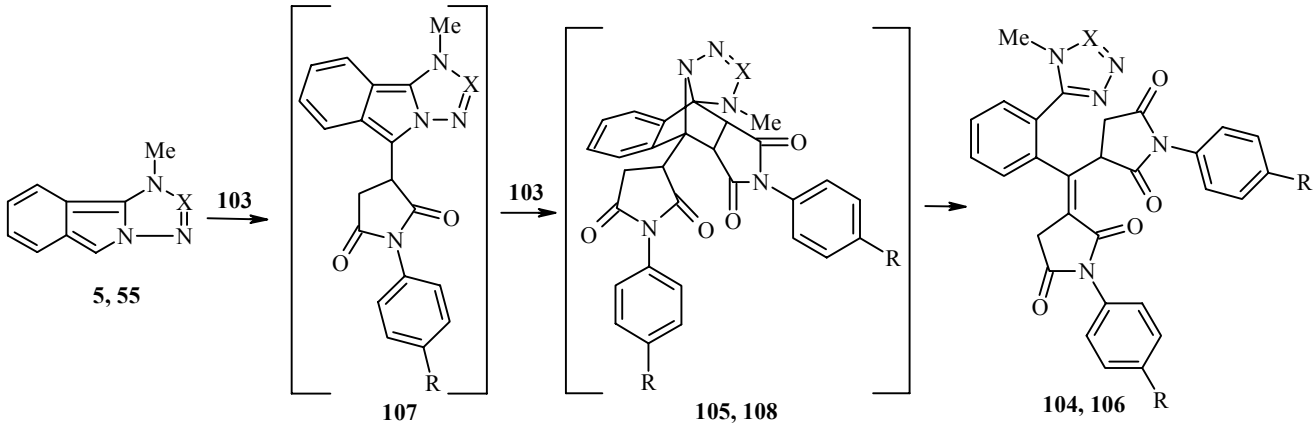
3.4. Cycloaddition Reactions

Cycloaddition involving condensed isoindoles containing a nodal nitrogen atom, unlike simple isoindoles [3], has been insufficiently investigated. On the basis of analysis of the static reactivity indices, however, high diene activity in the Diels–Alder reaction, close to the parent isoindole (see section 2), can be expected on the whole from triazolo- and tetrazoloisoindoles.



103

In the triazoloisoindole series cycloaddition has been investigated for the case of the reaction of compound **5** with *p*-anisylmaleimide **103** (R = OMe) [47]. According to elemental analysis and mass spectrometry, a 1:2 adduct with the supposed structure **104** (R = OMe) was obtained. Analysis of the ^{1}H NMR spectra of the unpurified products indicates formation of the Diels–Alder adduct **105** (R = OMe), which probably rearranges to compound **104** (R = OMe).



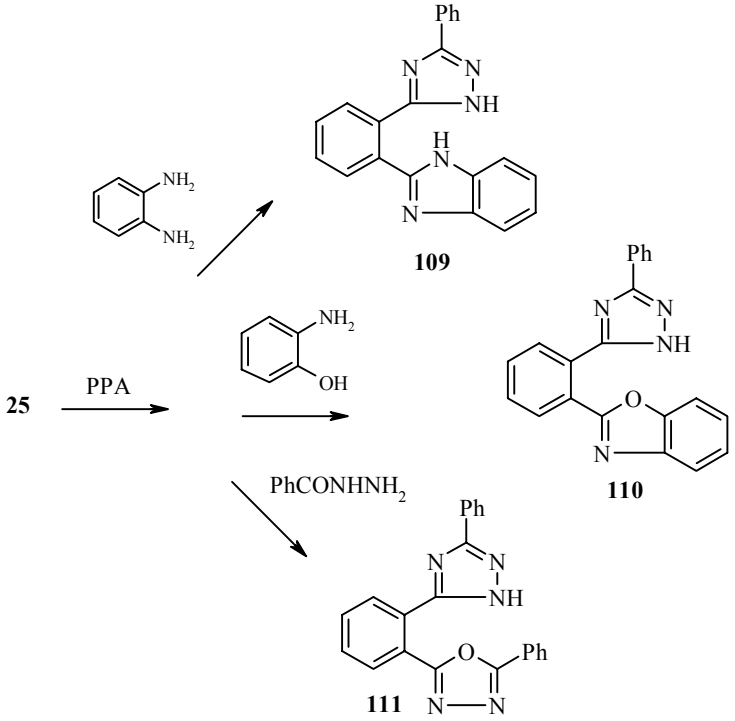
5, 55 **107** **105, 108** **104, 106**

5, 104, 105 X = CMe; **55, 106 – 108** X = N, R = Me

In the tetrazoloisoindole series cycloaddition has been investigated for the case of the reaction of compound **55** or its perchlorate **56** with the maleimides **103** (R = Me, NO_2) [48]. The reaction was carried out at various temperatures (from -10 to 110°C). In all cases, however, it took place ambiguously with the formation of a mixture of products. It was only possible to identify each of them (without isolation) by high-performance liquid chromatography using a UV detector. On the basis of these data it was suggested that the product **106** was formed through the intermediate compounds **107** and **108**.

3.5. Other Reactions

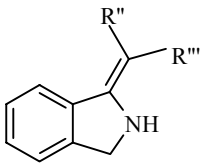
Compounds **25**, **28**, and **29** are unstable to the action of nucleophilic agents. For example, in the reaction of compound **25** with *o*-phenylenediamine, *o*-aminophenol, or benzohydrazide in polyphosphoric acid it is converted into compounds **109** (87%), **110** (85%), and **111** (75%) [16].



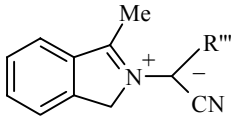
The action of *o*-phenylenediamine on the bistriazoloisoindoles **28** and **29** in polyphosphoric acid (~210°C) leads to opening of the pyrrolone ring with the formation of compound **109** [17].

The thermal stability of compounds **25**, **27-29** under vacuum (10^{-3}-$0.13\cdot10^{-2}$) and in water vapor was investigated. The release of CO_2, the amount of which increases significantly in the presence of water and with increase of temperature, during degradation indicates heterolytic cleavage of the *sym*-triazine ring, while the release of CO at 400-450°C indicates homolytic dissociation [49, 50].

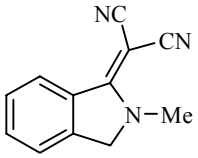
The *vic*-triazoloisoindoles **48b**,**c** are unstable and readily lose a molecule of nitrogen with increase in temperature, being converted into the isoindolinylidene derivatives **112a**,**b** (**a** R" = CN, R"' = COOMe, **b** R" = R"' = CN). The corresponding 1-methylisoindolinium methylides **113a**,**b** (**a** R"' = COOMe, **b** R"' = CN) are formed from compounds **48d**,**e** in deuterochloroform in the presence of trifluoroacetic acid. Thermal decomposition of the triazole **48e** leads to the product **114** – a homolog of isoindolinylidene-1-malononitrile **112b** [28].



112a,b

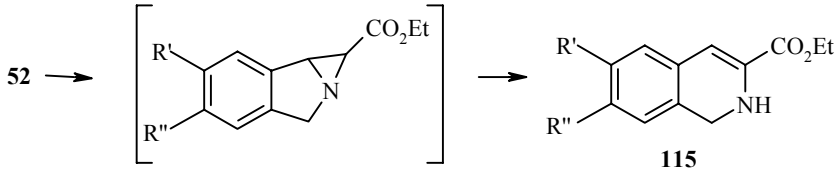


113a,b



114

As already mentioned above, compounds of type **51** isomerize on silica gel to the ethers **52**. The latter are transformed in benzene solution in the presence of rhodium acetate in the dark at room temperature into 3-(ethoxycarbonyl)-1,2-dihydroisoquinolines **115** [29].



Complexes of cyanine dyes of the tetrazoloisoindole series **86** and **67** with potassium hexacyanoferrate(III) and tetracyanonickelate(II) were synthesized for the first time [51, 52]. It should be noted that the complexes of cyanine dyes with metals have hardly been described at all in the literature, while the complexes of cyanine dyes of the isoindole series have not yet been studied.

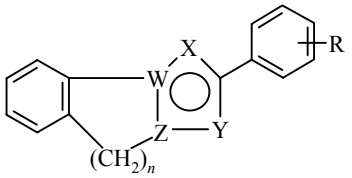
4. APPLICATIONS

The interest in triazolo- and tetrazoloisoindoles is due not only to the uniqueness of their properties but also to possible practical utilization of their derivatives.

4.1. Biological Activity

Contraceptive activity has been studied in 25 2-substituted 5H-1,2,4-triazoloisoindoles **8**, described in section 1.2. Strongest activity was exhibited by the 2-aryl-substituted compounds (R = Ph, *m*-$EtOC_6H_4$, *p*-ClC_6H_4, *p*-PhC_6H_4) [53-55].

Compounds of type **8** with others formed a new class of nonhormonal products with general formula **116**:



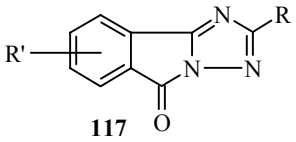
116

n = 1; 2; 2
X = Y = Z = N, W = C
Y = Z = N, X = W = C
X = W = N, Y = Z = C
X = Z = N, Y = W = C
Y = W = N, X = Z = C
R = H, *m*-EtO, *p*-Cl, *p*-Ph

The structure–activity relation was studied for these compounds, the contraceptive profile was described, the pharmacokinetic–activity relation was investigated, and the initial products of metabolism were discussed [56, 57].

Compound **8** (R = *m*-$EtOC_6H_4$) was also proposed for the treatment of skin complaints [58].

It was established that triazoles of type **117** inhibit inflammatory processes and/or are immunomodulators. They were proposed as agents for the treatment of psoriasis and rheumatoid arthritis [59].



117

R = H, Alk; R' = H, Alk, OMe

In trials on mice the tetrazoles **60a-e** at a dose of 200 mg/kg live weight have a depressing action on the central nervous system, while compound **60a** at a dose of 40-100 mg/kg has an anticonvulsive effect [36].

4.2. Cyanine Dyes

Cyanine dyes containing triazolo- and tetrazoloisoindole fragments (see sections 3.1, 3.3) have been inadequately investigated; their NMR spectra have not been published, and their fluorescence spectra have not been studied. However, such structures are regarded as promising from the standpoint of practical applications [60].

4.3. Polymers

Heat-resistant "staircase" polymers containing a 1,2,4-triazoloisoindole ring (see section 1) have found use in modern aircraft industry and in space technology [1]. As mentioned above, such polymers involve a combination of dianhydrides of type **30** and bisamidrazones. As a result of initial low-temperature condensation high-molecular film-forming poly(*o*-carboxy)benzoylamidrazones are formed. Solid-phase cyclodehydration of these polymers give polytriazoloisoindolones insoluble in organic and acidic solvents, not softening at 400°C, and undergoing degradation only at 450°C [19-21, 61]. The thermodynamics of the synthesis of these polymers were investigated [62]. The electric, photoconducting, and paramagnetic characteristics of polytriazoloisoindolones [63] and also their gradual degradation under the influence of external factors [64] were studied.

Recently great interest has been aroused in the chemical modification of natural polymers by the introduction of new functional groups. This has made it possible to create specific sorbents for the removal of metals from the organism and polymeric supports for biologically active preparations, and they can also be used in chromatographic analysis. The chemical modification of cellulose by tetrazoloisoindole derivatives of type **73** (Y = O, R = Me, Ph, *p*-MeC_6H_4) was investigated [65].

REFERENCES

1. F. S. Babichev and V. A. Kovtunenko, *Chemistry of Isoindole* [in Russian], Naukova Dumka, Kiev (1983).
2. F. S. Babichev, V. A. Kovtunenko, and A. K. Tyltin, *Usp. Khim.*, **50**, 2073 (1981).
3. V. A. Kovtunenko and Z. V. Voitenko, *Russ. Chem. Rev.*, **63**, 997 (1994).
4. W. L. Mosby, *Heterocyclic Systems with Bridgehead Nitrogen Atoms*, Pt. 1-2, Interscience, New York, London, (1961) (A series of monographs, A. Weissberger, *The Chemistry of Heterocyclic Compounds*).
5. M. M. Romanov, Yu. L. Briks, and F. S. Babichev, *Visn. Kyiv. Univ., Khimiya*, No. 18, 40 (1977).
6. F. S. Babichev, Yu. L. Briks, and N. N. Romanov, *Ukr. Khim. Zh.*, **47**, 291 (1981).

7. V. A. Kovtunenko, Z. V. Voitenko, V. L. Sheptun, L. I. Savranskii, A. K. Tyltin, and F. S. Babichev, *Khim. Geterotsikl. Soedin.*, 340 (1989).
8. Gruppo Lepetit S. p. A., Germ. Patent 2424670; *Chem. Abs.*, **83**, 206286 (1975).
9. F. S. Babichev, Yu. L. Briks, and N. N. Romanov, USSR Inventor's Certificate 771105; *Byull. Izobr.*, No. 38, 139 (1980).
10. F. S. Babichev, Yu. L. Briks, and N. N. Romanov, *Ukr. Khim. Zh.*, **47**, 735 (1981).
11. F. S. Babichev, Yu. L. Briks, and N. N. Romanov, USSR Inventor's Certificate 919313; *Byull. Izobr.*, No. 46, 227 (1983).
12. F. S. Babichev, Yu. L. Briks, and N. N. Romanov, *Ukr. Khim. Zh.*, **51**, 94 (1985).
13. B. Singh, *J. Am. Chem. Soc.*, **91**, 3670 (1969).
14. A. M. Mehta, S. R. Pednekar, M. S. Mayadeo, and K. D. Deodhar, *Indian J. Chem.*, **26B**, 1130 (1987).
15. V. V. Korshak, A. L. Rusanov, S. N. Leont'eva, and T. K. Dzhashiashvili, *Izv. Akad. Nauk. GSSR. Ser. Khim.*, 103 (1976).
16. V. V. Korshak, A. L. Rusanov, S. N. Leont'eva, and T. K. Dzhashiashvili, *Izv. Akad. Nauk. GSSR. Ser. Khim.*, 376 (1976).
17. V. V. Korshak, A. L. Rusanov, S. N. Leont'eva, and T. K. Dzhashiashvili, *Khim. Geterotsikl. Soedin.*, 1569 (1974).
18. V. V. Korshak and A. L. Rusanov, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 2661 (1968).
19. V. V. Korshak, A. L. Rusanov, S. N. Leont'eva, and T. K. Dzhashiashvili, *Soobshch. Akad. Nauk GSSR*, **72**, 357 (1973).
20. H. Kersten and G. Meyer, *Makromol. Chem.*, **138**, 265 (1970).
21. A. L. Rusanov, S. N. Leont'eva, T. K. Dzhashiashvili, and V. V. Korshak, *Vysokomol. Soed.*, **17**, 228 (1975).
22. A. A. Hassan, N. K. Mohamed, A. A. Aly, and A. F. E. Mourad, *Pharmazie*, **52**, 23 (1997).
23. P. C. Wade, B. R. Vogt, and T. P. Kissick, US Patent 4076823; *Chem. Abs.*, **88**, 190920 (1978).
24. P. C. Wade and T. P. Kissick, US Patent 4093728; *Chem. Abs.*, **89**, 163599 (1978).
25. P. C. Wade, T. P. Kissick, B. R. Vogt, and B. Toeplitz, *J. Org. Chem.*, **44**, 84 (1979).
26. F. S. Babichev, N. N. Romnov, and V. M. Shmailova, *Ukr. Khim. Zh.*, **42**, 1159 (1976).
27. N. N. Romanov, V. P. Shmailova, and F. S. Babichev, *Ukr. Khim. Zh.*, **45**, 860 (1979).
28. P. Kolsaker, P. O. Ellingsen, and G. Woeien, *Acta Chem. Scand.*, **B32**, 683 (1978).
29. J. M. Liu, J. J. Young, Y. J. Li, and Ch. K. Sha, *J. Org. Chem.*, **51**, 1120 (1986).
30. M. Bertrand, J. P. Dulcere, and M. Santelli, *Tetrahedron Lett.*, 1783 (1977).
31. J. P. Dulcere, M. Tawil, and M. Santelli, *J. Org. Chem.*, **55**, 571 (1990).
32. F. S. Babichev and N. N. Romanov, *Ukr. Khim. Zh.*, **39**, 49 (1973).
33. F. S. Babichev, N. N. Romanov, and V. P. Shmailova, *Ukr. Khim. Zh.*, **42**, 1213 (1976).
34. M. K. Eberle, L. Brzechffa, and W. J. Houlihan, *J. Org. Chem.*, **42**, 894 (1977).
35. M. K. Eberle and W. J. Houlihan, *Tetrahedron Lett.*, 3167 (1970).
36. W. J. Houlihan and M. K. Eberle, US Patent 3642814; *Chem. Abs.*, **76**, 140839 (1972).
37. R. Bonnett and K. Okolo, *J. Porphyrins Phthalocyanines*, **3**, 530 (1999).
38. A. H. Khuthier and J. C. Robertson, *J. Org. Chem.*, **35**, 3760 (1970).
39. V. A. Kovtunenko, Z. V. Voitenko, L. I. Savranskii, A. K. Tyltin, and F. S. Babichev, *Khim. Geterotsikl. Soedin.*, 51, 976 (1985).
40. V. A. Kovtunenko, Z. V. Voitenko, L. I. Savranskii, A. K. Tyltin, and F. S. Babichev, *Khim. Geterotsikl. Soedin.*, 216 (1988).
41. G. G. Dyadyusha, M. L. Dekhtyar, Yu. L. Briks, and N. N. Romanov, *Dyes and Pigments*, **17**, 29 (1991).
42. F. S. Babichev and N. N. Romanov, *Ukr. Khim. Zh.*, **41**, 719 (1975).
43. R. M. Claramunt, J. Elguero, A. Fruchier, and M. J. Nye, *Afinidad*, **34**, 545 (1977).

44. F. S. Babichev and M. M. Romanov, *Visn. Kyiv. Univ., Khimiya*, No. 18, 36 (1977).
45. A. I. Kisil, T. V. Egorova, and Z. V. Voitenko, in: *XIX Ukrainian conference on organic chemistry*. Book of abstracts, L'vivs'ka politekhnika, Lvov, (2001), p. 196.
46. A. I. Kisil, T. V. Egorova, and Z. V. Voitenko, in: *II Ukrainian conference of students and aspirants "Actual problems in chemistry"*, Kiev (2001), p. 67.
47. T. V. Egorova and Z. V. Voitenko, in: *International conference "Chemistry of nitrogen-containing heterocycles"*. Book of abstracts, Kharkov, (2000), p. 89.
48. T. B. Egorova, Z. V. Voitenko, R. V. Karbovska, V. A. Kishchenko, and V. K. Semenovich, in: *XIX Ukrainian conference on organic chemistry*. Book of abstracts, L'vivs'ka politekhnika, Lvov, (2001), p. 196.
49. V. V. Korshak, S. A. Pavlova, P. N. Gribkova, L. A. Mikadze, and A. L. Rusanov, *Izv. Akad. Nauk. GSSR. Ser. Khim.*, 313 (1976).
50. V. V. Korshak, S. A. Pavlova, P. N. Gribkova, L. A. Mikadze, A. L. Rusanov, L. Kh. Plieva, and T. V. Lekae, *Izv. Akad. Nauk. SSSR. Ser. Khim.*, 1381 (1977).
51. T. V. Egorova, Z. V. Voitenko, I. V. Zatovsky, and J. G. Wolf, in: *XX International Chugaev Conference on Coordination Chemistry* (Abstracts) [in Russian], Izd. Rost. Un-ta, Rostov-on-Don (2001), p. 220.
52. T. V. Egorova, Z. V. Voitenko, I. V. Zatovsky, and J. G. Wolf, in: *XV Ukrainian conference on inorganic chemistry with participation of foreign scientists.* Book of abstracts, Kyivskyi universitet, Kiev (2001), p. 135.
53. G. Galliani and L. J. Lerner, *Amer. J. Vet. Res.*, **37**, 263 (1976).
54. L. J. Lerner, G. Galliani, P. Carminati, and M. C. Moska, *Nature*, **256**, 130 (1975).
55. L. J. Lerner, in: *Recent Adv. Primatol (Congr. Intern. Primatol. Soc., 6 th.)*, **4**, 155 (1976) (Publ. 1978); *Chem. Abs.*, **91**, 102681 (1979).
56. G. Galliani, T. Cristina, U. Guzzi, A. Omodei-Sale, and A. Assandri, *J. Pharm. Dyn.*, **5**, 55 (1982).
57. A. Assandri, A. Omodei-Sale, and G. Galliani, *Rev. Drug. Metab. Drug. Interact.*, **4**, 237 (1982).
58. C. Rossi, PCT Int. Appl. WO 98/55118, 10.12.98; *Chem. Abs.*, **130**, 57206 (1999).
59. S. Albrechtsten, J. Hansten, E. Langvad, E. Eriksoo, K. Johansson, and K. E. Lundvall, PCT Int. Appl. WO 94/17068; *Chem. Abs.*, **121**, 205364 (1994).
60. A. A. Ishchenko, *Structure and Luminescence-Spectral Characteristics of Polymethine Dyes* [in Russian], Naukova Dumka, Kiev (1994).
61. V. V. Korshak, A. L. Rusanov, S. N. Leont'eva, and T. K. Dzhashiashvili, *Macromolecules*, **8**, 582 (1975).
62. N. V. Karyakin, V. N. Sapozhnikov, A. L. Rusanov, V. V. Korshak, S. N. Leont'eva, M. G. Gverdtsiteli, and D. S. Tugushi, *Izv. Akad. Nauk. GSSR. Ser. Khim.*, 271 (1989).
63. V. S. Voishchev, A. L. Ruslanov, S. N. Leont'eva, O. V. Kolninov, O. V. Voishcheva, and B. I. Mikhant'ev, *Vysokomol. Soedin. Ser. B*, **17**. 870 (1975).
64. A. N. Machyulis, A. L. Lipskis, and A. L. Rusanov, *Tr. Akad. Nauk LitSSR. Ser. B*, No. 4, 99 (1976).
65. S. V. Ryabov, Z. V. Voitenko, S. M. Kobilinskii, S. V. Laptii, T. V. Egorova, and A. I. Kisil, in: *XIX Ukrainian conference on organic chemistry.* Book of abstracts, L'vivs'ka politekhnika, Lvov (2001), p. 378.