*Chemistry of Heterocyclic Compounds, Vol. 40, No. 8, 2004*

# SYNTHESIS AND CHARACTERISTICS OF TETRACYCLIC SYSTEMS OF BENZO[*b*]FURO-INDOLES AND THEIR DERIVATIVES. (REVIEW)

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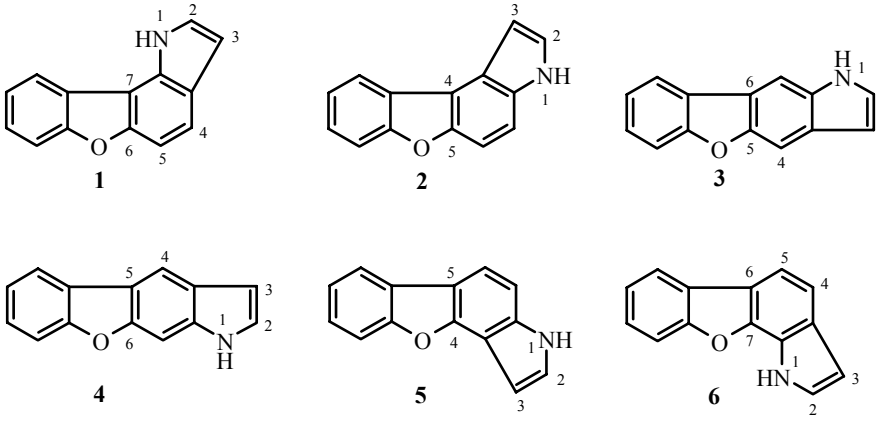
*Published data on the nomenclature, structure, synthesis, and chemical characteristics of benzo[b]furoindoles with a pyrrole ring fused at various positions in relation to initial tricyclic system of dibenzofuran are reviewed.*

**Keywords:** benzofurans, benzo[*b*]furoindoles, dioxobenzo[*b*]furoindoles, indoles, nomenclature, Japp–Klingemann reaction, Friedel–Crafts, Vilsmeier–Haack, Mannich, Fischer synthesis.

Data on unsubstituted benzo[*b*]furoindoles first appeared in 1984 [1, 2]. Substances with antibacterial activity, including high tuberculostatic activity, were found among their derivatives [3].

## 1. NOMENCLATURE AND STRUCTURE OF BENZO[*b*]FUROINDOLES

Over the course of time the nomenclature of the tetracyclic systems benzo[*b*]furoindoles has undergone considerable change. In [1, 2] names of type **A** were used: Indolo[7,6-*d*]benzo[*b*]furan (**A1**), indolo[4,5-*d*]-benzo[*b*]furan (**A2**), indolo[6,5-*d*]benzo[*b*]furan (**A3**), indolo[5,6-*d*]benzo[*b*]furan (**A4**), indolo[5,4-*d*]-benzo[*b*]furan (**A5**), and indolo[6,7-*d*]benzo[*b*]furan (**A6**).




**1** **2** **3** **4** **5** **6**

**A**

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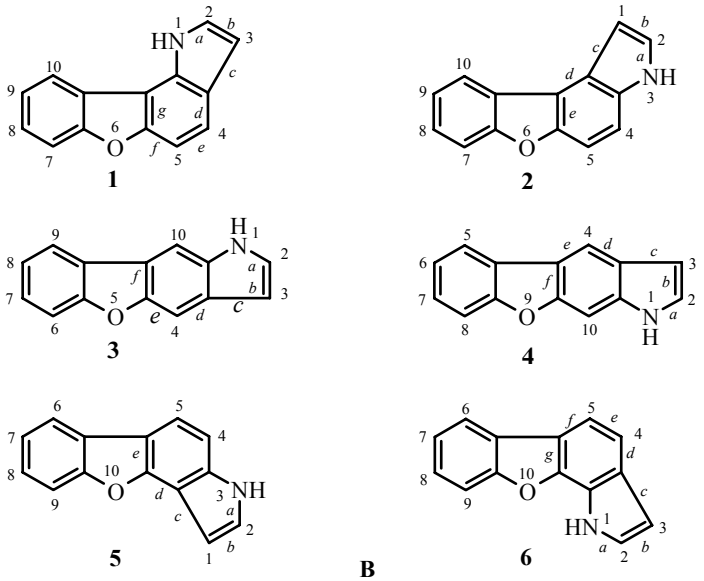
In contemporary literature new names of type **B**, which conform to the IUPAC nomenclature rules and the Ring Index, are used: 1H-benzo[*b*]furo[2,3-*g*]indole (**B1**), 1H-benzo[*b*]furo[3,2-*e*]indole (**B2**), 1H-benzo-[*b*]furo[2,3-*f*]indole (**B3**), 1H-benzo[*b*]furo[3,2-*f*]indole (**B4**), 1H-benzo[*b*]furo[2,3-*e*]indole (**B5**), and 1H-benzo[*b*]furo[3,2-*g*]indole (**B6**) [4-7].



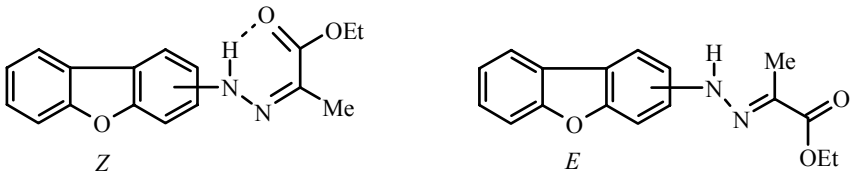

## 2. METHODS OF SYNTHESIS OF UNSUBSTITUTED BENZO[*b*]FUROINDOLES

The methods for the synthesis of benzo[*b]*furoindoles can be divided into two main groups: Syntheses based on the amino derivatives of dibenzofurans using the classical E. Fischer reaction [1, 2] and based on the reduction of dioxodihydrobenzo[*b*]furoindoles (obtained by the Sandmeyer method) with diborane in THF at -78°C [4-7].

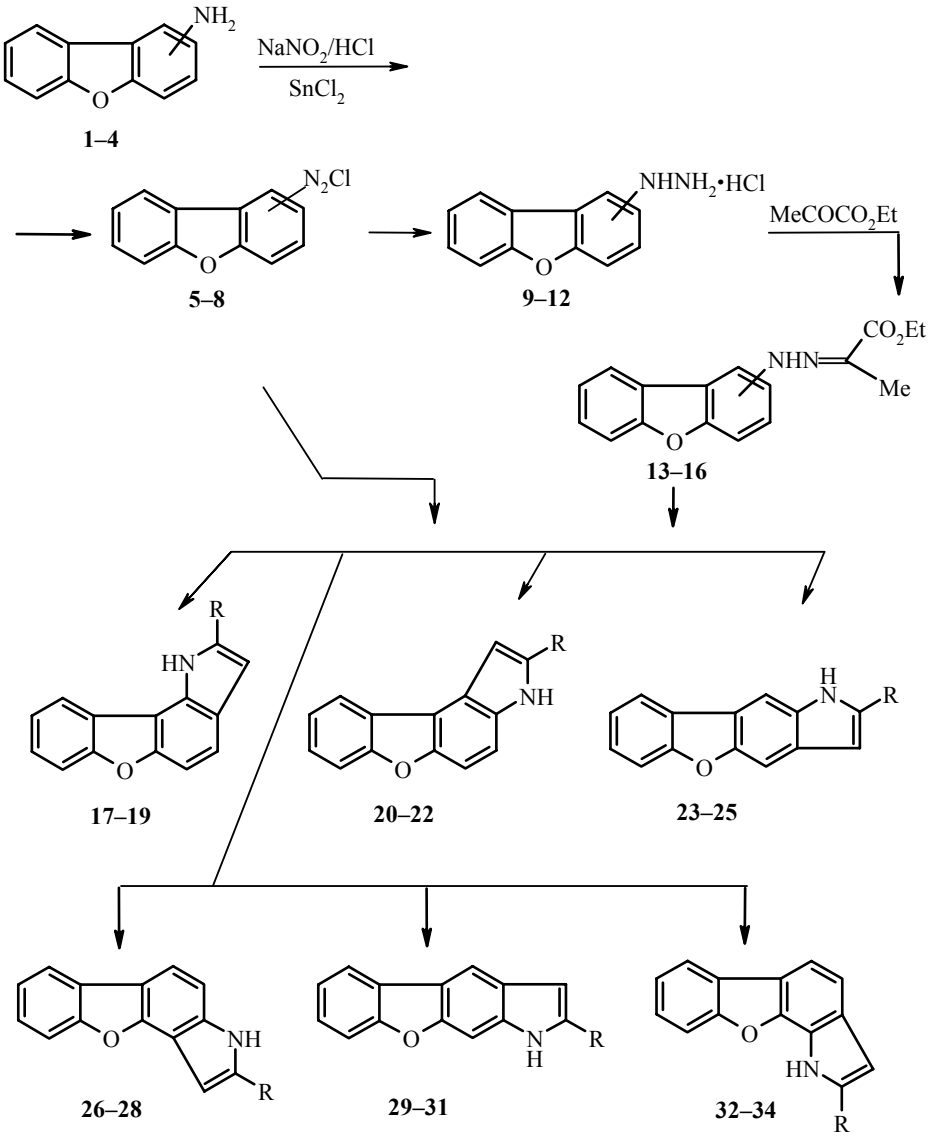
### 2.1. Syntheses Based on Amino Derivatives of Dibenzofurans

**2.1.1. Synthesis of Dibenzofuranylhydrazones of Ethyl Pyruvate.** Of all the methods widely used for the annelation of a pyrrole ring to various types of aromatic and heterocyclic systems (the Reissert, Madelung, Bischler, Fischer, Nenitzescu, Japp–Klingemann, and a series of other reactions [8-15]) the most suitable in the synthesis of benzo[*b*]furoindoles was the classical Fischer reaction and its modification based on the Japp–Klingemann reaction [1, 2] (Scheme 1).

The starting compounds were 1-, 2-, 3-, and 4-aminodibenzofurans **1**-**4**, which were transformed successively into the respective diazonium salts **5**-**8** and then into the hydrazine hydrochlorides **9**-**12**. The reaction of these hydrazines with ethyl pyruvate leads to the hydrazones **13**-**16**. These hydrazones exist as mixtures of *syn* (*Z*) and *anti* (*E*) forms with a preference for the latter.

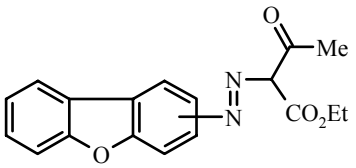


Scheme 1



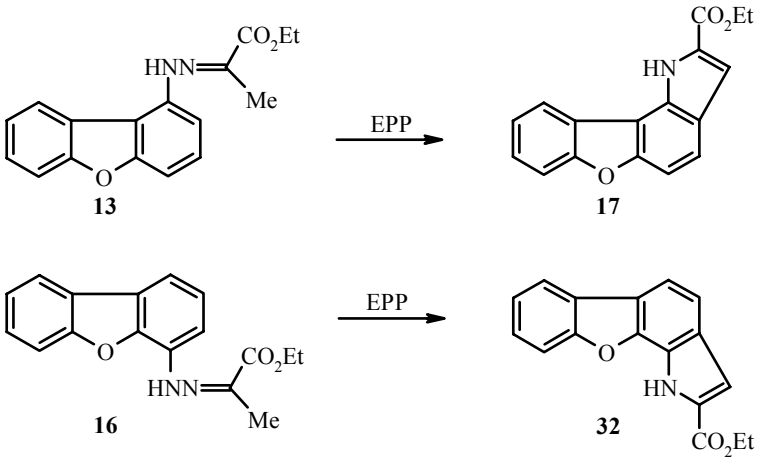

**17**, **20**, **23**, **26**, **29**, **32** R = $CO_2Et$; **18**, **21**, **24**, **27, 30**, **33** R = $CO_2H$; **19**, **22**, **25**, **28**, **31**, **34** R = H

If the Japp–Klingemann reaction (azo coupling of the respective diazonium salt with acetoacetic ester) is used for the production of the hydrazones **13-16**, the so-called azo esters [the ethyl esters of α-(dibenzofuranylazo)-α-acetylpropionic acids] are formed in addition to the mixture of isomeric hydrazones [3, 16-19]. They readily isomerize during the reaction to the respective hydrazones, but sometimes they can nevertheless be isolated and characterized [20, 21]:

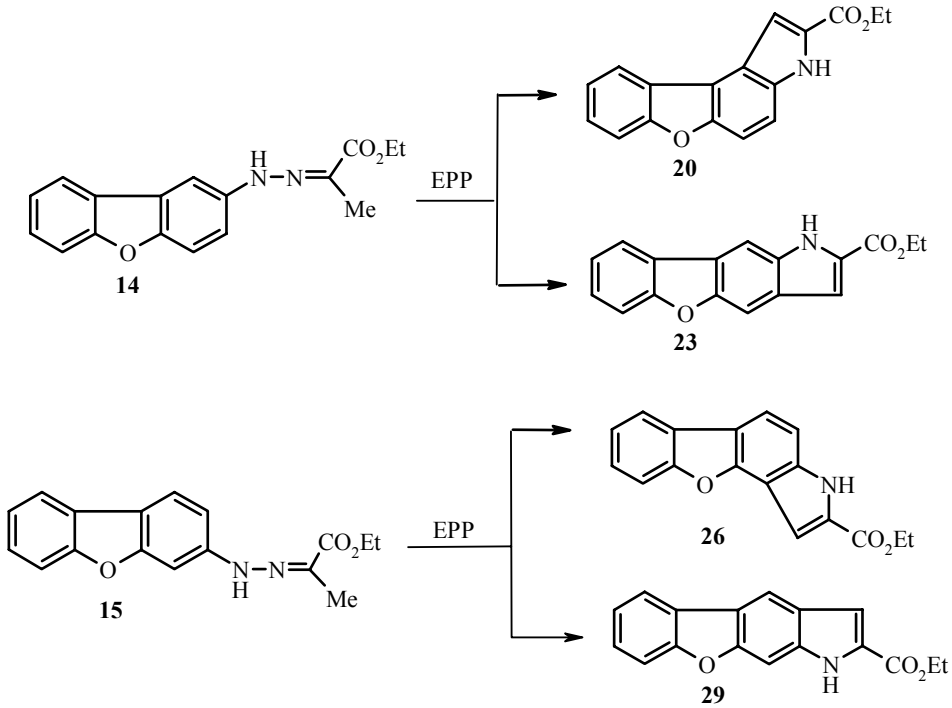


**2.1.2. Conditions for Indolization of the Dibenzylfurylhydrazones of Ethyl Pyruvate.** Among the numerous catalysts for the Fischer cyclization [Lewis acids, sulfuric acid in glacial acetic acid, polyphosphoric acid (PPA), alcohol solution of hydrogen chloride] ethyl polyphosphate (EPP) has proved most effective for the production of benzo[*b*]furoindoles [1, 2]. On the basis of spectral investigations it was established [3] that the *anti* form of the hydrazones undergoes cyclization.

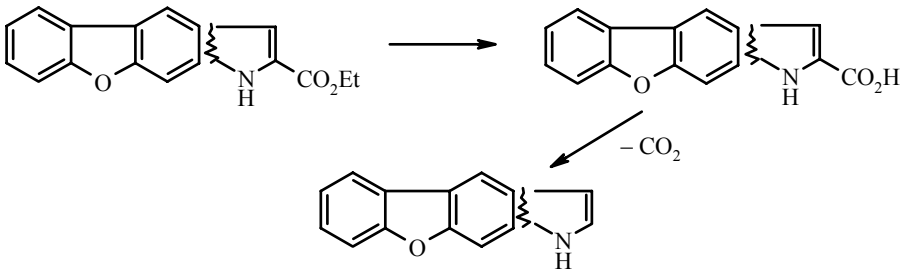
**2.1.3. Synthesis of Isomeric Benzo[*b*]furoindoles.** The cyclization of the 1- and 4-dibenzofuranylhydrazones (**13** and **16**) of ethyl pyruvate by the action of EPP leads to the formation of the corresponding angular ethyl benzo[*b*]furo[2,3-*g*]- and benzo[*b*]furo[3,2-*g*]indole-2-carboxylates (**17**) and (**32**):




Indolization of the 2- and 3-dibenzofuranylhydrazones of ethyl pyruvate (compounds **14** and **15**) gives a mixture of the corresponding linear and angular ethyl benzo[*b*]furo[3,2-*e*]- and benzo(*b*)furo[2,3-*f*]-, benzo[*b*]furo[2,3-*e*]-, and benzo[*b*]furo[3,2-*f*]-2-carboxylates **20** and **23**, **26** and **29** in equal proportions [3]:



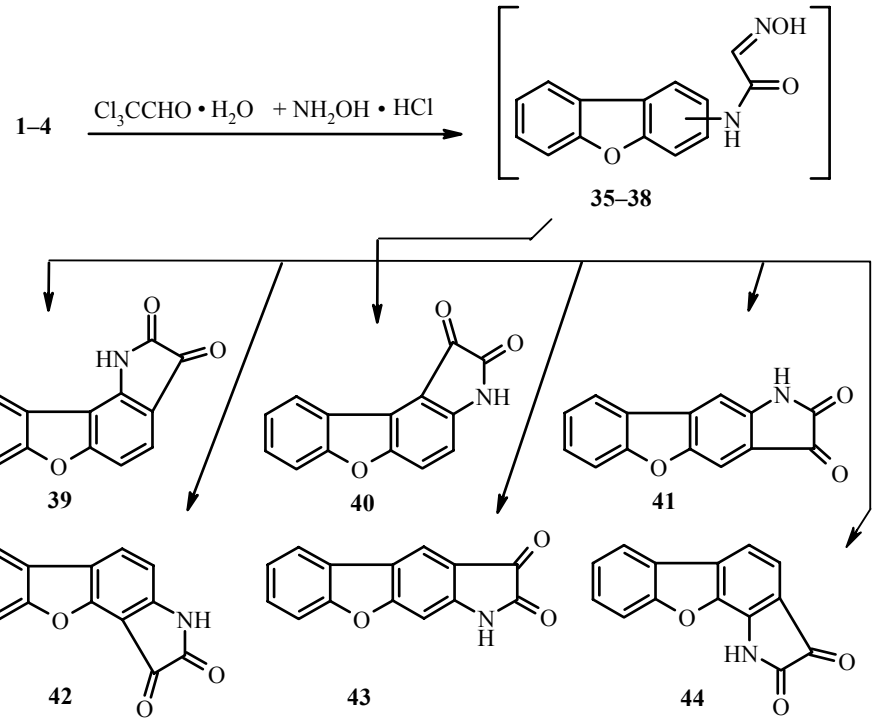
The carboxylic acids **18**, **21**, **24**, **27**, **30**, and **33** were obtained with quantitative yields by saponification of the respective esters **17**, **20**, **23**, **26**, **29**, and **32** with a water–alcohol solution of alkali, while the unsubstituted 1H-benzo[*b*]furoindoles **19**, **22**, **25**, **28**, **31**, and **32** were obtained by thermal decarboxylation of the acids in an inert gas atmosphere:



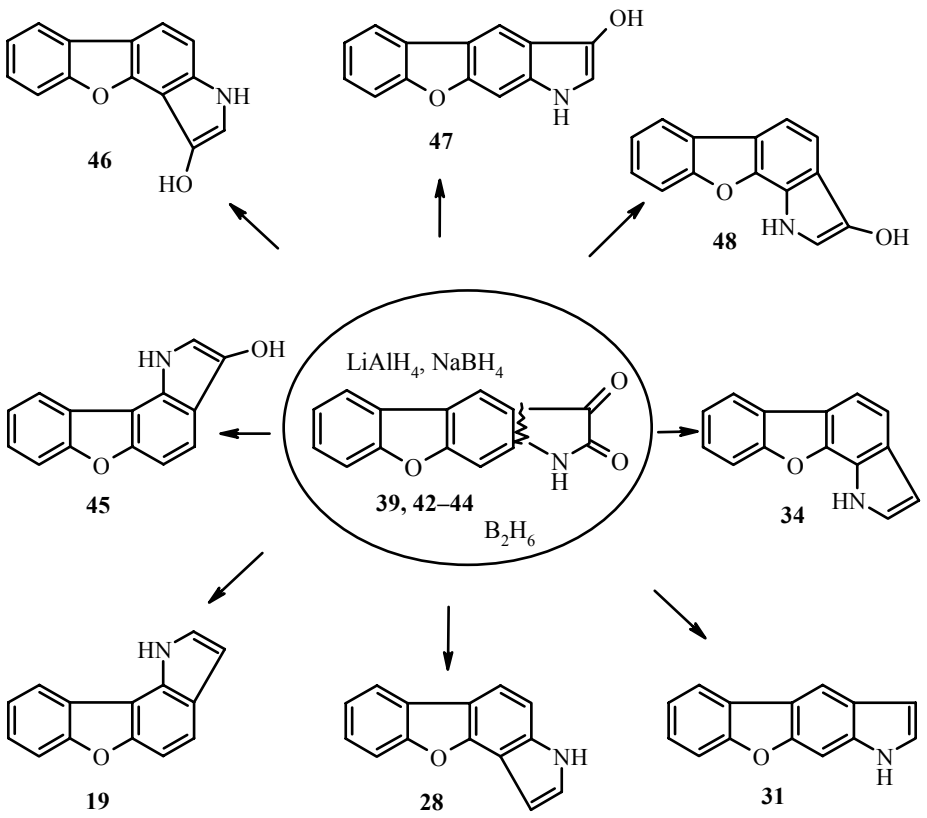

The criteria for the assignment of the synthesized structures to the angular and linear isomers on the basis of the $^1$H NMR spectra are given in [1, 2].

### 2.2. Syntheses Based on Dioxodihydrobenzo[*b*]furoindoles

Another original method, based on the use of dioxodihydro-1H-benzo[*b*]furoindoles (easily obtained by the Sandmeyer reaction) as starting compounds, was described for the construction of the tetracyclic system of benzo[*b*]furoindoles [4-7]. Reaction of the amino derivatives of dibenzofuran **1-4** with chloral hydrate and hydroxylamine hydrochloride in an acidic medium gave the corresponding isonitrosoacetamidodibenzofurans **35-38**, the cyclization of which in sulfuric acid led to the required compounds **39-44**:



The heterocyclic systems synthesized in this way are easily reduced to the corresponding indole systems, and the yields and the direction of the process depend on the choice of reducing agent. Thus, the action of lithium aluminum hydride in absolute pyridine gives a mixture of hydroxybenzo[*b*]furoindoles **45**-**48** (~40-50%), a small amount of unsubstituted benzo[*b*]furoindoles **19**, **28**, **31**, and **34**, and the unreacted original compounds **39**, **42**-**44**. The use of diborane in THF at -78°C as reducing agent gave acceptable yields of the corresponding unsubstituted benzo[*b*]furoindoles **19**, **28**, **31**, and **34** [4-7, 22].




The results agree fully with published data indicating that isatins are reduced readily and with quantitative yields to indoles [23], while indole itself is fairly resistant to diborane even at room temperature [24].

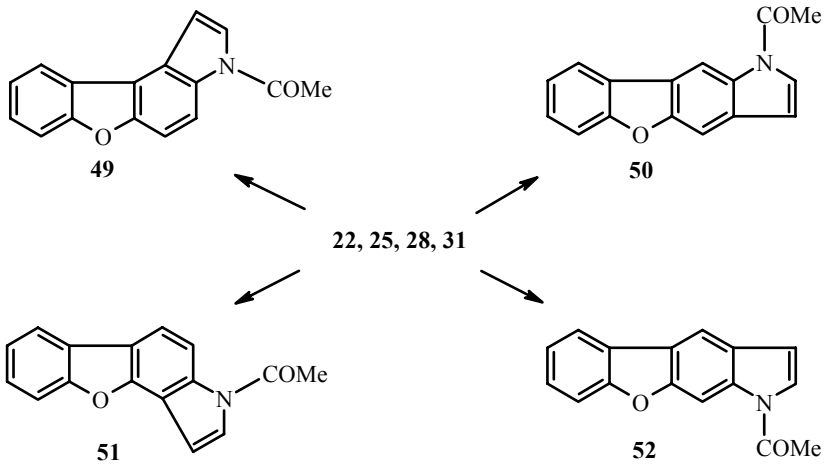
## 3. CHEMICAL PROPERTIES OF BENZO[*b*]FUROINDOLES

The behavior of the heterocyclic systems **19**, **22**, **25**, **28**, and **31** in some electrophilic substitution reactions typical of the indole system (acetylation, the Vilsmeier reaction, the Mannich reaction, and azo coupling) was described in [25, 26].

In view of the specific affinity of the heterocycles to indole and benzofuran, the obtained results were assessed in comparison with indole and dibenzofuran.

### 3.1. Acetylation

It was found that the behavior of the investigated heterocyclic systems during acetylation with acetic anhydride [25, 26] differs substantially from the behavior of indole under analogous conditions [27]. Thus, whereas indole forms a mixture of insignificant amounts of 1-acetyl- and 3-acetylindoles during treatment with pure acetic anhydride while the main product is 1,3-diacetylindole [27], under such conditions the benzo[*b*]furoindoles **22**, **25**, **28**, and **31** only form the N-acetyl derivatives [25, 26], and the reaction only takes place with prolonged boiling (20-30 h) in acetic anhydride.




The use of a mixture of acetic acid and acetic anhydride for the acetylation of benzo[*b*]furoindoles does not change the direction of the reaction.

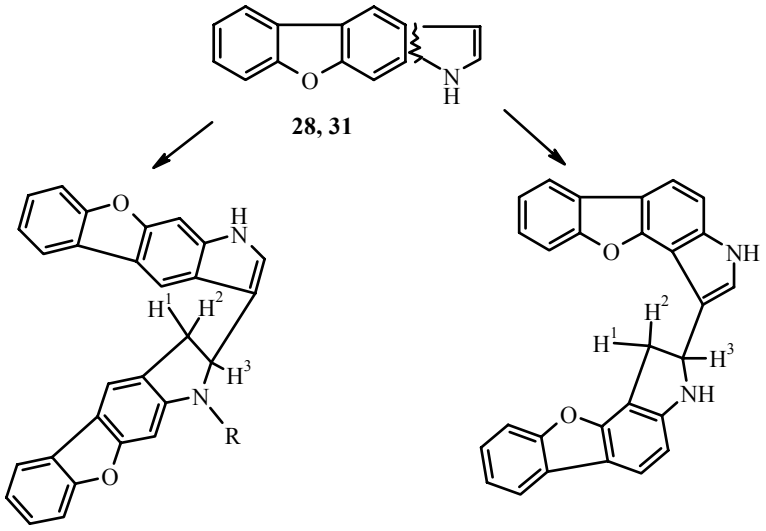
Data from the NMR, IR, and UV spectra fully support the structure of the synthesized acetyl derivatives [25, 26]. The nature of the initial fragmentation of the molecular ions of these compounds under electron impact does not depend on the type of fusion of the rings and involves the successive elimination COMe, $COCH_2$, HCN, CS, CO, Me, and other groups (depending on the structure of the compounds), and in some cases this is confirmed convincibly by the corresponding metastable transitions [25, 26].

It is convenient to discuss the acylation of benzo[*b*]furoindoles in the Friedel–Crafts reaction, like all the other chemical characteristics, in comparison with the behavior of indole and dibenzofuran under analogous conditions. It is generally known that unsubstituted indole is resinified in the presence of Lewis acids, 1,3-diacetylindole does not react at all with acetyl chloride in the presence of aluminum chloride [28, 29], while the acetylation of 1-acetyl-2,3-dimethylindole takes place in the benzene ring with the formation of the 6-acetyl derivative [30]. It is also known that in a sufficiently acidic medium indole forms dimers and trimers depending on the acidity of the medium [30, 31].

In the literature there data indicating that it is the substituted benzene ring in the tricyclic system of dibenzofuran that undergoes acetylation by acetyl chloride in the presence of aluminum chloride [32, 33].

In contrast to the behavior of unsubstituted indole and dibenzofuran, under Friedel–Crafts conditions the investigated compounds mainly form "dimerization products" with a small amount of the products from acetylation of the indolenine nitrogen atom of the dimer as impurity [34]. As in the case of the indoles [30, 31], this is determined by the ease of protonation of the system. It is interesting that the dimerization of linear benzo[*b*]furoindoles **25** and **31** takes place considerably more readily than that of the compounds with angular structure **22** and **28** [34]. The authors explain this fact by the different ease of protonation of the linear and angular structures, as was confirmed by kinetic investigations of azo coupling and by data from the $^1$H NMR spectra (the chemical shifts of the protons at the β-position of the pyrrole ring) [34]. In addition a substantial

role is probably also played by steric factors: The isomers with linear structures are sterically more accessible for the formation of dimers than the angular structures. The dimers are formed according to the following general scheme:

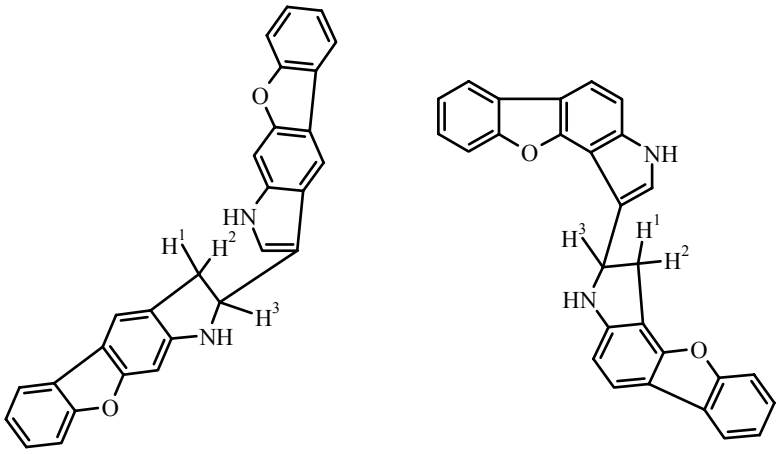


**28, 31**

**53a**, **54** **55a**

**53a** R = H, **54** R = COMe

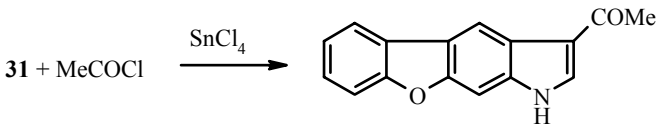
Depending on the reaction conditions [34], compounds **53b** and **55b** are also formed in addition to the isomers **53a** and **55a**, and the ratios of the obtained dimers **53a**-**53b** and **55a**-**55b** are 60:40 and 50:50 respectively:



**53b** **55b**

It was established experimentally that change in the reaction time substantially affects the ratio of the geometric forms in the case of the linear heterocycles **53a**,**b** and does not affect the ratio of the isomeric dimers with angular structure **55a**,**b** [34]. Thus, if the duration of the reaction of benzo[*b*]furoindole **31** with acetyl chloride in the presence of aluminum chloride is increased to 2.5-3 h the stereoisomer **53b** is fully converted into the stereoisomer **53a**. The formation of a small amount of the N-acetyl derivative **54** as impurity is also observed under these conditions.

In the case of compound **31** it was shown that the dimer is not formed if the weaker Lewis acid $SnCl_4$ is used in the Friedel–Crafts reaction, but the product from acetylation at the β-position of the pyrrole ring in the tetracyclic system **56** is formed smoothly [35]:

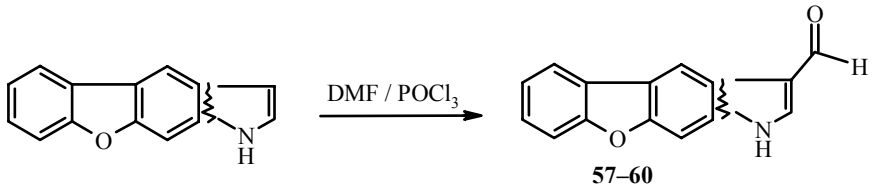



**56**

### 3.2. The Vilsmeier Reaction

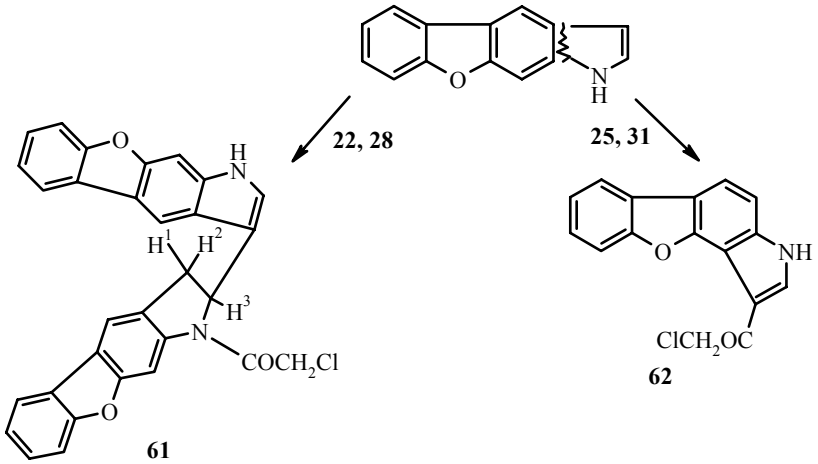
One of the reactions most widely used for the synthesis of the carbonyl derivatives of indole is the Vilsmeier–Haack reaction [36]. The indole derivatives produced by this reaction are of interest both from the biological standpoint and as intermediate compounds for the synthesis of a whole series of physiologically active substances [37-45].

This was the process that was used for the production of formyl and acetyl derivatives of 1H-benzo[*b*]furoindoles [25, 26, 46]. The standard Vilsmeier complex N,N-DMF–$POCl_3$ was used as formylating agent. In the given case, as also for the indole derivatives [45], formylation takes place smoothly at the β position of the pyrrole ring of the 1H-benzo[*b*]furoindoles [25, 26]:




**57–60**

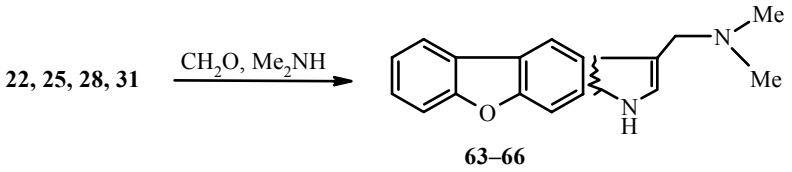
N,N-Dimethylacetamide and N,N-diethylchloroacetamide with phosphorus oxychloride were used as reagents for Vilsmeier acetylation. It was found that in reaction with the N,N-diethylacetamide complex the tetracyclic systems with linear structure **25** and **31** give chlorine-substituted dimers, and as in the case of the Friedel–Crafts reaction substitution takes place at the nitrogen atom of the hydrogenated pyrrole ring [34]. The heterocycles with angular structure **22** and **28**, like pyrrolocarbazole [47], lead mainly to the product from chloroacetylation at the β-carbon atom of the pyrrole ring.




**61** **62**

### 3.3. The Mannich Reaction

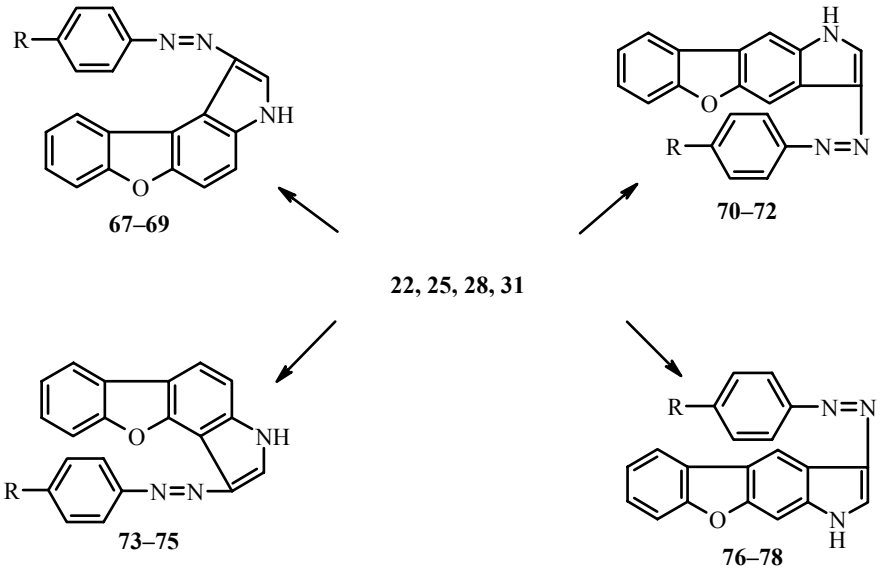
The N,N-dimethylaminomethyl derivatives of benzo[*b*]furoindoles are formed readily and with almost quantitative yields in the reaction of compounds **22**, **25**, **28**, and **31** with formaldehyde and an aqueous solution of dimethylamine under the conditions described for indole [48]. It was shown that the reaction takes place unambiguously at the β-position of the pyrrole ring both for the linear and for the angular isomers of benzo[*b*]furoindoles [25, 26].




**63–66**

### 3.4. The Azo Coupling Reaction

The effect of weak electrophiles on the course of electrophilic substitution in the benzo[*b*]furoindole series was investigated for the case of the most selective reagents – benzene- and 4-chloro- and 4-nitrobenzenediazonium chlorides [26]. In view of some structural similarity between the indicated heterocyclic systems and indole the reaction was conducted under the usual conditions for indole [49-52]. As for indole, the most suitable reaction medium was a neutral medium, in which the azo coupling process took place without any significant problems. True, the azo coupling with the above-mentioned diazo components takes place readily and fairly smoothly, but the reaction rate and the yields of the azo coupling products bear a distinct relationship to the nature of annelation of the pyrrole ring and the nature of the electrophile. Thus, for example, benzo[*b*]furoindoles with linear structure **25** and **31** enter into azo coupling considerably more readily than the corresponding isomers with angular structure **22** and **28**.




**67, 70, 73, 76** R = H, **68, 71, 74, 77** R = *p*-Cl, **69, 72, 75, 78** R = *p*-$NO_2$

As expected, the largest yields were obtained in the reaction of the heterocyclic systems with *p*-nitrobenzenediazonium chloride, and the smallest yields were obtained with benzenediazonium chloride [25, 26]. A more detailed analysis of the behavior of isomeric benzo[*b*]furoindoles was made in [53], which gives a quantitative assessment of the role of annelation of the pyrrole ring in relation to the dibenzofuran system based on kinetic data on the reaction of the isomeric structures with weak and, consequently, selective electrophilic reagents, i.e., arenediazonium fluoroborates.

Thus, the published data examined above demonstrate that the synthesis route: tricyclic dibenzofuran system → nitro derivative → amine → hydrazine → hydrazone → cyclic ester → cyclic acid → unsubstituted tetracyclic benzo[*b*]furoindole system [1,2], together with the use of dihydroxy-1H-benzo[*b*]furoindoles as starting compounds [4-7] make it possible to obtain not only new heterocyclic systems but also to synthesize from them a series of derivatives that are of practical interest.

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