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4H-3,1-BENZOXAZINES, THEIR SALTS AND DIHYDRO DERIVATIVES. (REVIEW)

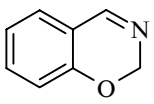
E. V. Gromachevskaya, F. V. Kvitkovskii, T. P. Kosulina, and V. G. Kul'nevich

Data from published sources and the authors' own investigations on the synthesis, chemical characteristics, spectral characteristics, and structure of 4H-3,1-benzoxazine derivatives are reviewed. The prospects for their practical utilization are demonstrated.

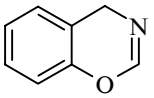
Keywords: benzoxazines, dihydrobenzoxazines, benzoxazinium salts, synthesis, chemical characteristics, spectral characteristics.

The 1,3- and 3,1-benzoxazines are bicyclic systems in which a 1,3-oxazine ring is annellated with a benzene ring.

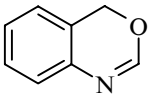
There are three possible isomers of 1,3(3,1)-benzoxazine and two isomers of dihydro-1,3(3,1)-benzoxazine:



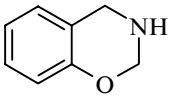
2H-1,3-benzoxazine



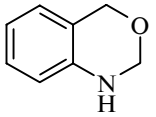
4H-1,3-benzoxazine



4H-3,1-benzoxazine



3,4-dihydro-2H-1,3-benzoxazine



1,4-dihydro-2H-3,1-benzoxazine

Such systems have been known since the end of the nineteenth century. However, the authors of a few existing reviews [1-5] restricted themselves to listing the described syntheses and transformations, whereas wider study of these compounds is of considerable interest. The characteristics of benzoxazines are largely determined by the geometry of the 1,3-oxazine ring and the mutual influence of the heterocyclic and aromatic fragments. In accordance with the foregoing we considered it useful to analyze the literature on the synthesis, properties, and spectral characteristics of 4H-3,1-benzoxazines, 3,4-dihydro-2H-3,1-benzoxazines, and their salts.

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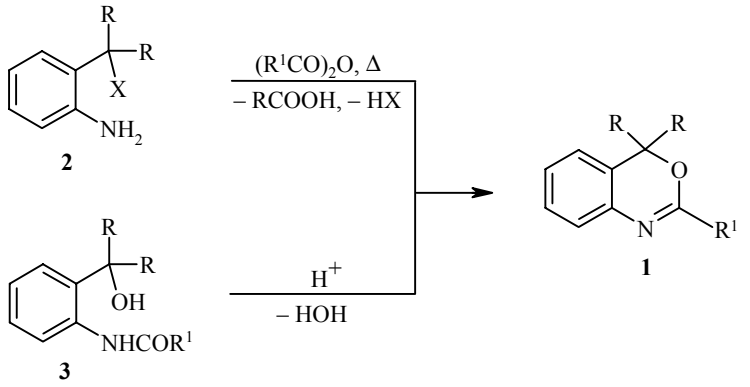
1. METHODS OF SYNTHESIS AND CHARACTERISTICS OF 4H-3,1-BENZOXAZINES AND THEIR SALTS

1.1. Synthesis and Characteristics of 4H-3,1-Benzoxazines and Benzoxazinium Salts

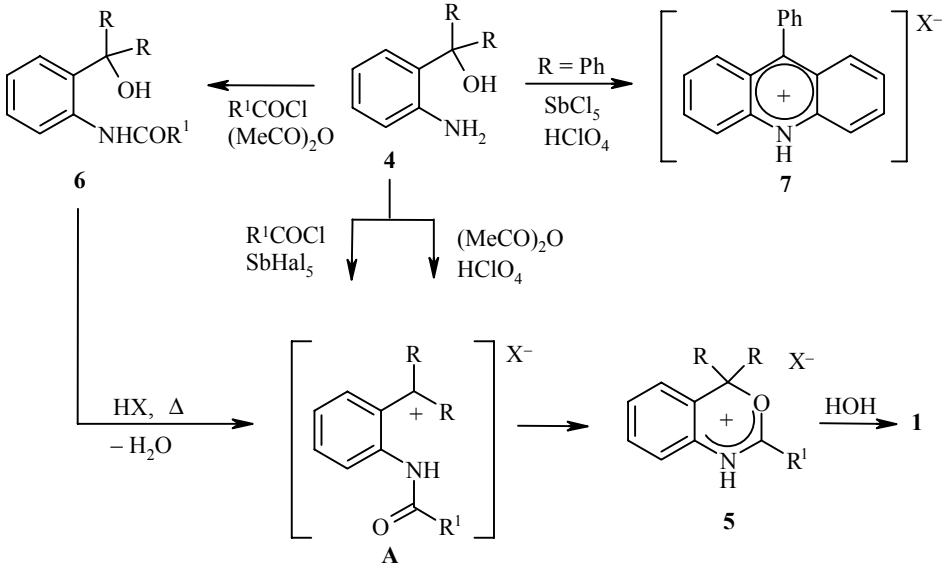
In most cases *o*-aminobenzyl alcohols or *o*-aminobenzyl halides **2** and also acylamino alcohols [3] are used as starting materials for the synthesis of substituted 4H-3,1-benzoxazines **1** [6-12].



X = OH, Hal; R = H, R^1 = Me, Et, Ph, *p*-$MeOC_6H_4$; R = Me, R^1 = Me, Et, Ph; R = Ph, R^1 = Me, Ph; R = *p*-$Me_2NC_6H_4$, R^1 = Me, OEt

The acylation of tertiary *o*-aminophenylcarbinols **4** followed by their heterocyclization in an acidic medium to 2,4-substituted 4H-3,1-benzoxazines **1** through the corresponding salts **5** has been investigated in greatest detail [13-16].

With acid anhydrides and chlorides in the cold the carbinols **4** form the amido alcohols **6**, which give the 4H-3,1-benzoxazinium salts **5** when heated in an excess of the acylating agents [14]. The yield of the salts, which contain a furan fragment, is less that 50%, which is explained by the instability of the furan compounds on heating in the acidic medium. A method for their production through the corresponding perchlorates [15] and



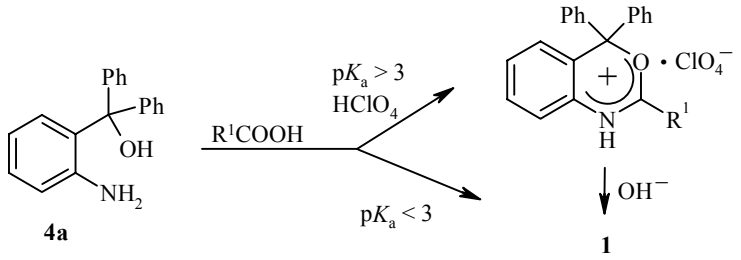
R = Me, Ph; R^1 = Me, Ph, fur-2-yl, 5-bromofur-2-yl; X = Cl, ClO_4, $SbHal_6$; Hal = Cl, F

hexahaloantimonates [13], which are formed with higher yields than the chlorides by the action of condensing agents (perchloric acid, Lewis acids) at room temperature, was therefore proposed for the 4H-3,1-benzoxazines (including those containing a furan substituent). Treatment of the salts **5** with aqueous alkali leads to the bases **1**.

The benzoxazinium salts **5** can be formed by heterocyclization of the cation **A**, which is produced during the dehydration of the amido alcohol **6**. The proposed scheme is confirmed by the synthesis of the corresponding benzoxazinium salts from *o*-(acetylamino)phenyldiphenylcarbinol **6** (R^1 = Me) and also agrees with the mechanism of the formation of monocyclic analogs of the 4H-3,1-benzoxazinium salts – 5,6-dihydro-4H-1,3-oxazinium salts [17-19].

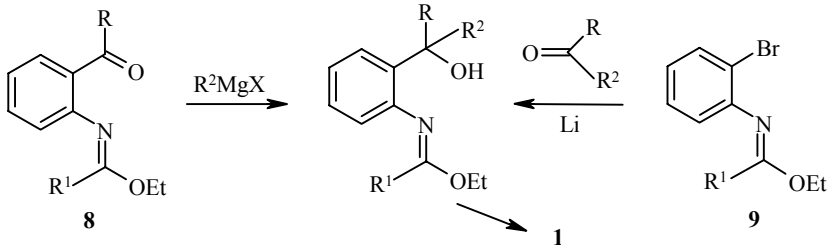
A necessary condition for the production of the salts **5** is a twofold excess of the acylating agent. In the case of *o*-aminophenyldiphenylcarbinol **4a** an insufficient amount of the acylating agent in an acidic medium leads to the formation of the acridinium salt **7** [13].

The reaction of the carbinol **4a** with carboxylic acids as acylating agents was studied with a view to synthesizing 4H-3,1-benzoxazines by a more accessible method making it possible to extend the range of products significantly [15, 16]. The conditions for the reaction of the carbinol **4a** with the acid are determined by the strength of the acid. Thus, for acids with $pK_a \geq 3.0$ the benzoxazine structures are formed according to a general scheme through the perchlorates. If the strength of the acid is higher (e.g., for haloacetic acids) heterocyclization to the desired compounds takes place in the absence of perchloric acid:



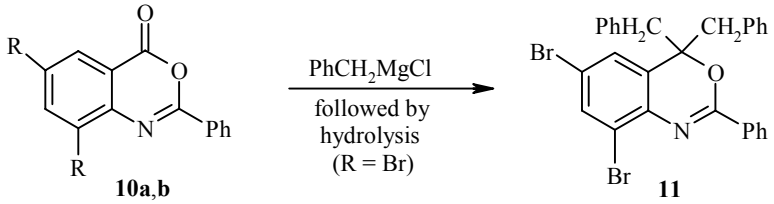
R^1 = Pr, CHBrEt, $CH_2Cl(I)$, CCl_3, CF_3, 2(3)-nitrophenyl, β-(fur-2-yl)vinyl, 5-chlorofur-2-yl, 5-nitrofur-2-yl

There are a number of nontraditional methods for the synthesis of 4H-3,1-benzoxazines, based on the reactions of the imidates **8**, **9** [20, 21], benzoxazinones [9, 22, 23], or quinazolones [9] with organometallic compounds.



R, R^1, R^2 = Alk, Ar

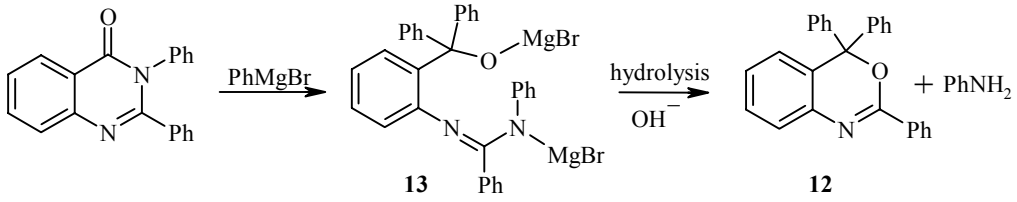
The benzoxazin-4-ones [9, 22, 23] react with Grignard compounds to form various products, depending on the nature of the reagent. Thus, the reaction of compounds **10a**,**b** with phenylmagnesium bromide and ethylmagnesium iodide leads to cleavage of the heterocycle [9, 22]. However, in the reaction of the benzoxazinone **10b** with benzylmagnesium chloride 4,4-dibenzyl-6,8-dibromo-2-phenyl-3,1-benzoxazine **11** is formed as the main product [22].



10a,**b** **11**

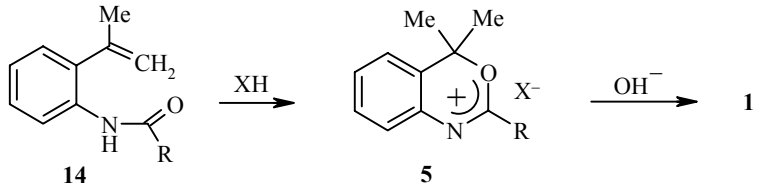
10 a R = H, **b** R = Br

The action of Grignard compounds on substituted derivatives of 4-quinazolone [9] also leads to various products with opening of the heterocycle. It was shown that 2,3-diphenyl-4-quinazolone reacts with phenylmagnesium bromide to form 2,4,4-triphenyl-4H-3,1-benzoxazine (**12**) and aniline through the intermediate **13**.



13 **12**

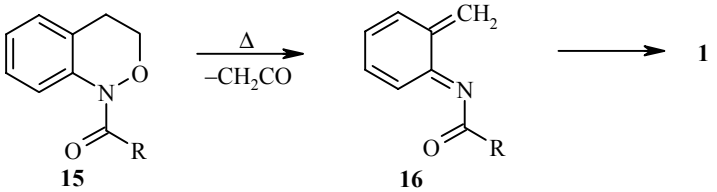
The acyl derivatives of *o*-isopropenylaniline **14** undergo cyclization in an acidic medium to derivatives of 4H-3,1-benzoxazine **1** through the corresponding salts **5** [24].



14 **5**

R = Ph, Me, CH_2Ph (with R = Ph the yields were quantitative), X = Cl, $SbCl_6$, F_3CCOO

The thermal decomposition of N-acyl-3,4-dihydro-1H-2,1-benzoxazines **15**, involving the loss of formaldehyde and subsequent intramolecular Diels–Alder reaction of the obtained N-acylazaxylylenes **16**, leads to 2-substituted 4H-3,1-benzoxazines **1** [25].

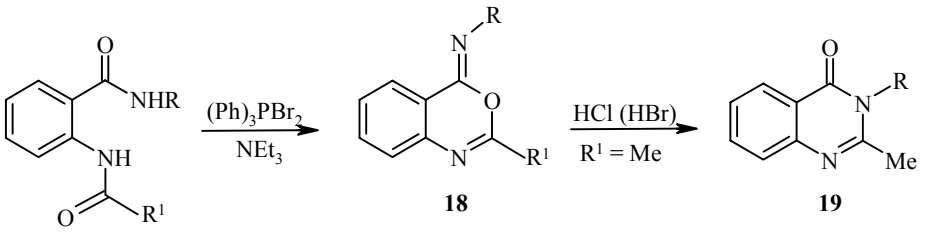


15 **16**

R = Alk, Ph

The transformation of 1,4-dihydro-2H-3,1-benzoxazines to 4H-3,1-benzoxazines on heating in acylating agents was described [26]. More detail about this is given in section 2.2.

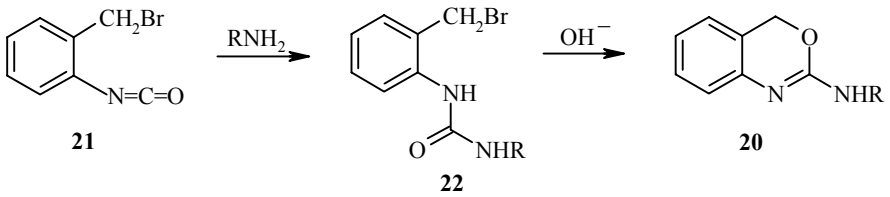
Methods for the production of 4H-3,1-benzoxazines attached to a heteroatom (N, S) at the second or fourth positions of the heterocycle are known [27-33]. Thus, 4-imino-4H-3,1-benzoxazines **18** were obtained from N-acylanthranilamides **17**; their 2-methyl-substituted derivatives are capable of rearranging to 4-quinazolinones **19** under the influence of HCl (or HBr) [27].



17 **18** **19**

R = Alk, Ph

A method was developed for the synthesis of 2-alkyl(aryl)amino-4H-3,1-benzoxazines **20** with high yields (60-70%) by the reaction of 2-bromomethylphenyl isocyanates **21** with amines [30] followed by cyclization of the obtained substituted ureas **22** in a basic medium.

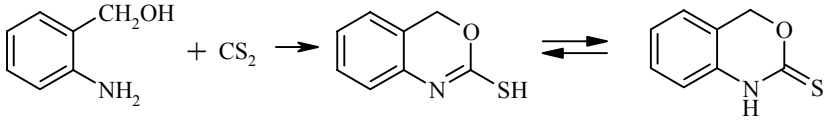


21 **22** **20**

R, R1 = Alk, Ar

N-Substituted 2-amino-4H-3,1-benzoxazines are also produced during the reaction of *o*-aminobenzyl alcohols with isocyanates [29, 31, 32] with diphenyl N-cyanocarbonimidate followed by treatment of cyanoimido-substituted compounds with amines [28].

2-Mercapto-4H-3,1-benzoxazine (**23**) is formed during the treatment of *o*-aminobenzyl alcohol with carbon disulfide [33]. It exists preferentially in the 4H-3,1-benzoxazine-2(1H)-thione form.

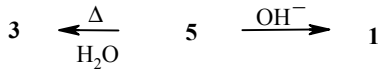


23

1.2. Properties of 4H-3,1-Benzoxazinium Salts

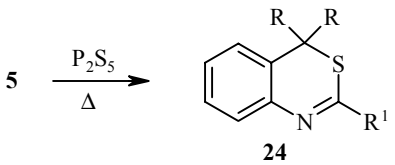
The properties of 4H-3,1-benzoxazinium salts, produced by reactions both in the heterocyclic fragment of the molecules and in the aromatic ring, have been described [7, 8, 13-16, 19].

1.2.1. Hydrolysis and Deprotonation. Most of the salts are hydrolyzed in water, forming N-acyl derivatives of *o*-aminobenzyl alcohol of type **3** [7, 8]. In basic aqueous media the 4H-3,1-benzoxazinium salts **5** undergo deprotonation, the conditions of which are determined by the structure of the anion. Thus, the trihalides are readily converted into the corresponding 4H-3,1-benzoxazines **1** in aqueous ammonia or 5% sodium carbonate solution in the cold [14], into the perchlorates when heated in aqueous ammonia [15], and into the hexachloroantimonates when boiled in a 10% solution of alkali [13].



R = Alk, Ar; R1 = Alk, Fur; X = Hal, ClO_4, $SbCl_6$

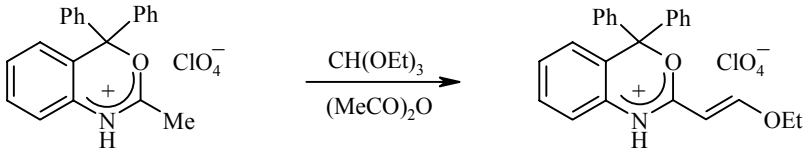
1.2.2. Transition to Benzothiazines. The transition to benzothiazine systems [24] is realized by treating the 4H-3,1-benzoxazinium hydrohalides **5** with phosphorus pentasulfide [8, 14]. Furyl-substituted benzothiazines were first obtained in this way [14].



24

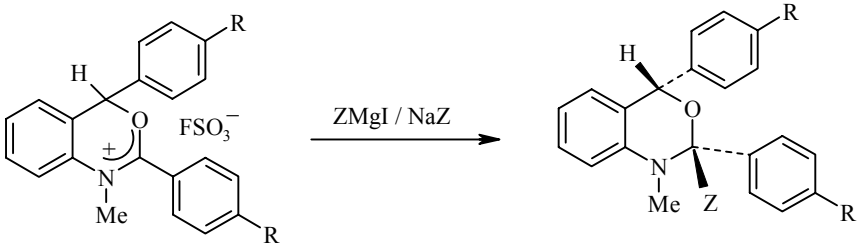
R = H, Ph; R^1 = Me, Ph, Fur; Hal = Cl, Br

1.2.3. Reactions at the 2-CH_3 Group. It was established that 2-methyl-4,4-diphenyl-4H-3,1-benzoxazinium perchlorate (**25**) exhibits weak C–H acidity in the 2-methyl group under the influence of the $\tilde{C}\text{–}\overset{+}{\tilde{N}}\text{–}\tilde{O}$ fragment, forming the corresponding ethoxyvinyl derivative (**26**) [15].



25 **26**

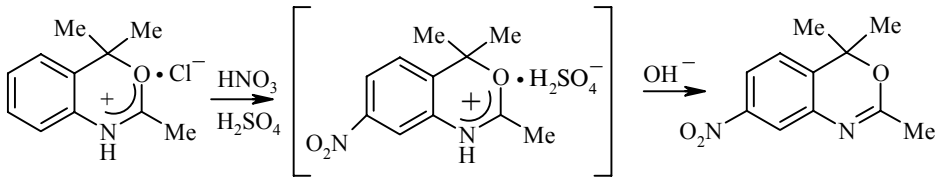
1.2.4. Reactions at the *meso* Carbon Atom of the Heterocycle. Reactions at the *meso*-carbon atom of the heterocycle with such nucleophiles as sodium ethoxide, methylmagnesium iodide, and sodium cyanide leading to the formation of substituted 1,2-dihydro-4H-3,1-benzoxazines **28** with the *cis* arrangement of the aryl groups have been described for substituted 1-methyl-4H-3,1-benzoxazinium fluorosulfonates **27** [34].



27 **28**

R = H, Alk, Hal; Z = OEt, Me, C≡N

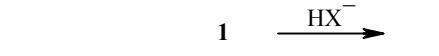
1.2.5. Nitration in the Aromatic Ring. The treatment of 2,4,4-trimethyl-4H-3,1-benzoxazinium hydrochloride (**29**) with a nitrating mixture leads to the mononitro-substituted product **30** with retention of the heterocycle [14]:



29 **30**

1.3. The Properties of 4H-3,1-Benzoxazines

Like their dihydro derivatives, 4H-3,1-benzoxazines are organic bases [7, 8] stable in a basic medium; with protic acids they form salts [4, 13-15]:

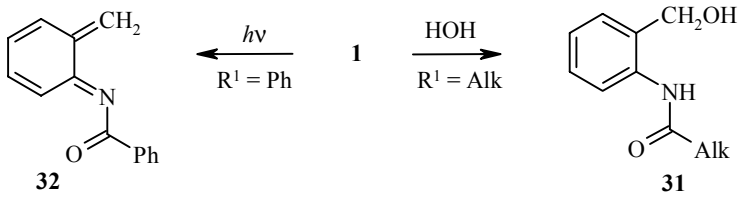


R = Alk, Ph; R^1 = Alk, Ar, Fur; X = Hal, ClO_4

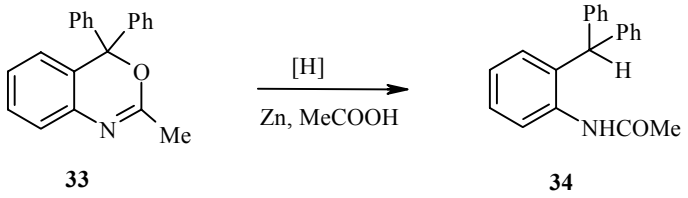
For 4H-3,1-benzoxazines reactions taking place both with opening and with retention of the heterocycle have been described. The former include hydrolysis [25] and the reactions of benzoxazines with reducing agents [7] and with nucleophilic reagents [35, 36].

Hydrolysis of substituted 4H-3,1-benzoxazines **1** is determined by the presence and character of substituents in the heterocycle. For example, 2-alkyl-4H-3,1-benzoxazines readily undergo hydrolysis, forming *o*-hydroxymethylanilides **31** [25].

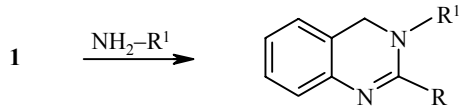
2-Phenyl-4H-3,1-benzoxazine is relatively stable toward hydrolysis but is capable of photochemical cleavage of the heterocycle with the formation of N-benzoylazaxylylene **32** [25].



The reduction of 2-methyl-4,4-diphenyl-4H-3,1-benzoxazine (**33**) with zinc dust in acetic acid leads to *o*-acetylaminophenyldiphenylmethane (**34**) [7].



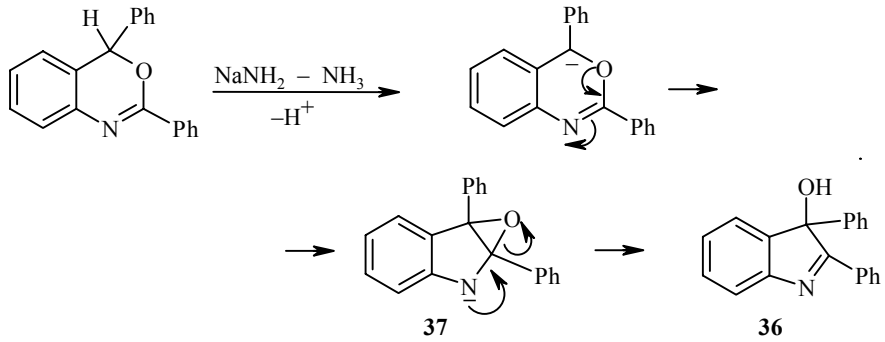
3,4-Dihydroquinazolines **35** are formed in the reaction of 4H-3,1-benzoxazines with amines and hydrazines [35, 36].



35

R = Alk, Ar, N–Ar; R^1 = NH_2, Alk, Ar

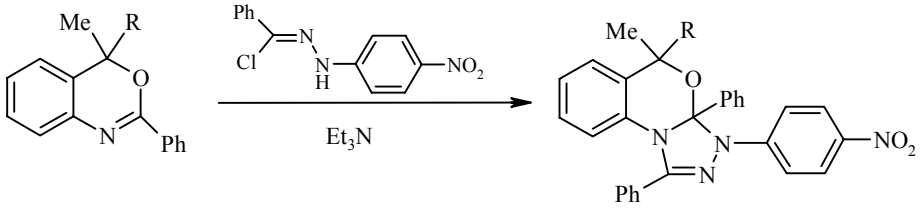
In the $NaNH_2$–NH_3 system the heterocycle in 2,4-diphenyl-4H-3,1-benzoxazine is contracted, leading to 3-hydroxy-3H-indole **36** [5, 34].



37 **36**

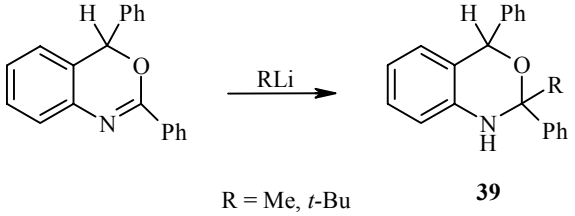
The authors of [34] assume that this transformation takes place through the intermediate indole 2,3-oxide anion **37** by an intramolecular Wittig rearrangement. This rearrangement also takes place in the case of 1,2-dihydro-4H-3,1-benzoxazines (see section 2.2).

1,3-Dipolar addition at the C=N bond of 4H-3,1-benzoxazines leads to the formation of the stable tricyclic adduct **38** [24].



38

The structure of the benzoxazine **38** is confirmed by the results of stereochemical and crystallographic investigations [24]. Similar reactions also include the reduction of 4H-3,1-benzoxazines to 1,4-dihydro-2H-3,1-benzoxazines **39** using organolithium compounds [34].



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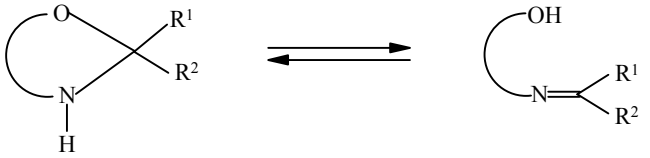
2. THE SYNTHESIS AND PROPERTIES OF THE DIHYDRO DERIVATIVES OF 4H-3,1-BENZOXAZINES

2.1. The Synthesis of 1,4-Dihydro-2H-3,1-benzoxazines

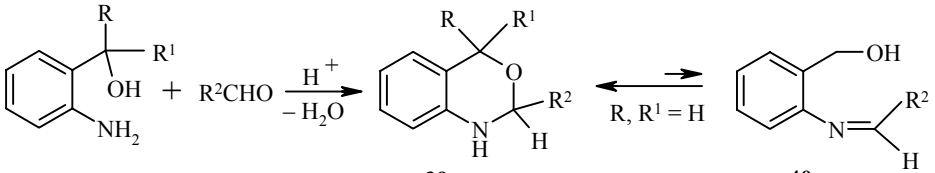
The main method for the production of 1,4-dihydro-2H-3,1-benzoxazines is the condensation of *o*-aminobenzyl alcohols with carbonyl compounds using various solvents and acidic catalysts [5, 11, 37-40].

These compounds were first obtained in 1892 [37]. The condensation of the reagents was conducted in a boiling benzene solution in the presence of acetic acid. In view of the absence at that time of methods of spectral analysis the authors of the paper assumed that azomethines were formed here.

More recent investigations [38, 41-45] have shown that 1,3-oxazolidines and related systems (tetrahydrooxazines, perhydrobenzoxazines, and dihydrobenzoxazines) can exist in the cyclic form or an alternative linear form (a Schiff base).



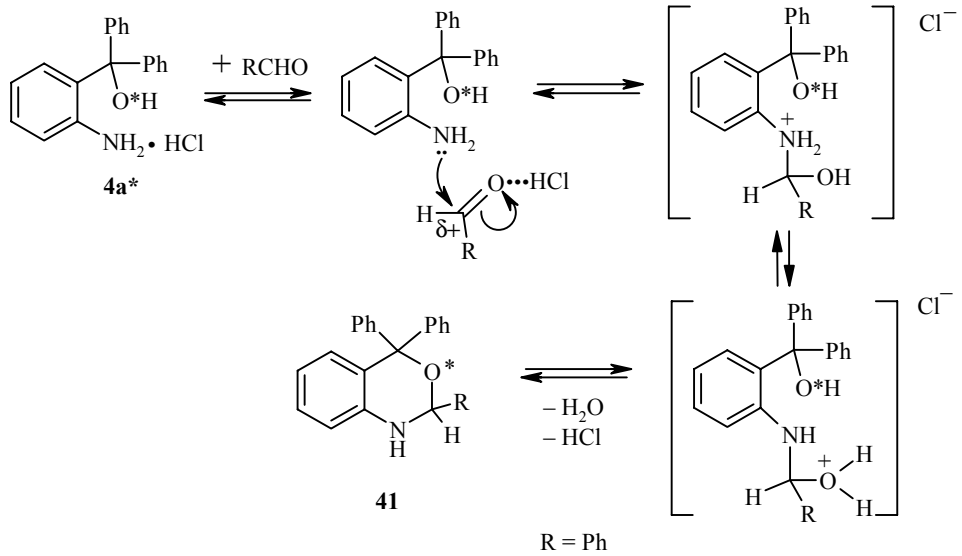
In [38, 44] it was demonstrated on the basis of spectral and chemical data that the products of the investigated condensation were 1,4-dihydro-2H-3,1-benzoxazines **39**. However, it was established that dihydrobenzoxazines can exist in tautomeric equilibrium with the azomethines **40** [41, 46].



39 **40**

R, R^1 = H, Me, Ph; R^2 = Et, Pr, C_5H_{11}, C_6H_{13}, $CHPh_2$, CH(Ph)C≡N, CH_2Ph, Ph, *p*-$MeOC_6H_4$, *p*-$Me_2NC_6H_4$, *p*-$O_2NC_6H_4$, *p*-ClC_6H_4, thien-2-yl, fur-2-yl, pyrr-2-yl, *p*(*o*)-HOC_6H_4, *o*-$MeOC_6H_4$, COPh, *p*-$Me_2NC_6H_4CH$=CH

The mechanism of the formation of 2,4-substituted 1,4-dihydro-2H-3,1-benzoxazines was investigated by means of labeled atoms according to the data from ^{17}O NMR spectroscopy and mass spectrometry [47, 48]. The introduction of the isotopic oxygen label into the molecule of *o*-aminophenyldiphenylcarbinol **4a*** during investigation of its reaction with benzaldehyde made it possible to conclude that the oxygen atom of the hydroxyl group in the reaction product **41*** comes from the initial carbinol. This confirms the mechanism of heterocyclization of the investigated compounds, according to which nucleophilic addition of the amino group of the carbinol **4a*** at the >C=O bond of the aldehyde takes place initially with the subsequent elimination of water and the formation of a molecule of 2,4,4-triphenyl-1,2-4H-3,1-benzoxazine (**41***). The labeled carbinol **4a*** was brought into reaction with benzaldehyde in the form of the hydrochloride in boiling benzene. The released gaseous HCl served as catalyst of the reaction [48].

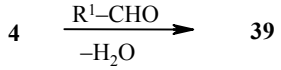


4a* **41**

R = Ph

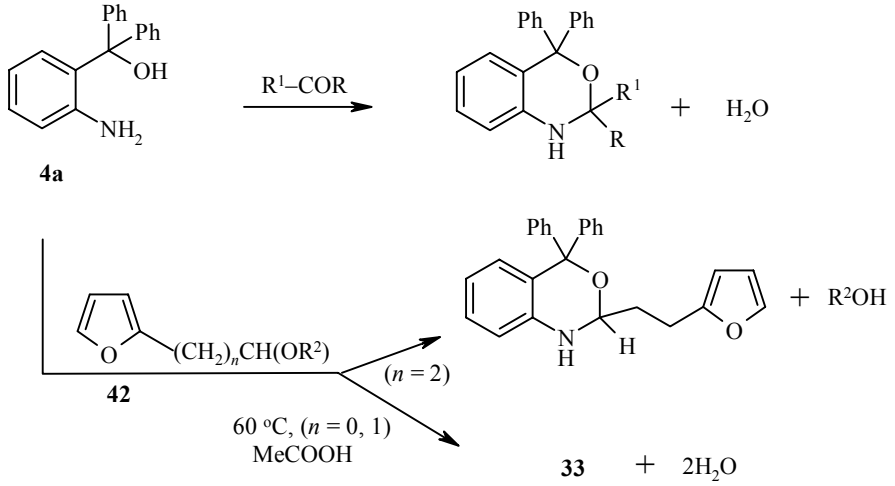
The most suitable medium for the production of dihydrobenzoxazines from tertiary *o*-aminophenylaminocarbinols was acetic acid, which acts both as solvent and as catalyst [26, 49, 50]. By realizing the condensation at room temperature it was possible to obtain previously difficultly obtainable furyl-substituted dihydrobenzoxazines [26, 49].

It was established that substituted *o*-aminophenylcarbinols **4** react with aldehydes of any structure with the formation of the corresponding dihydrobenzoxazines **39** [26, 49, 50].



R = Ph, Me, CH_2CH_2Ph; R^1 = Me, Pr, CH=CHMe, CH=CHPh, β-(5-methylfur-2-yl)ethyl, 5-bromofur-2-yl, 5-nitrofur-2-yl, 5-dimethylaminofur-2-yl, 5-nitrothien-2-yl, CCl_3

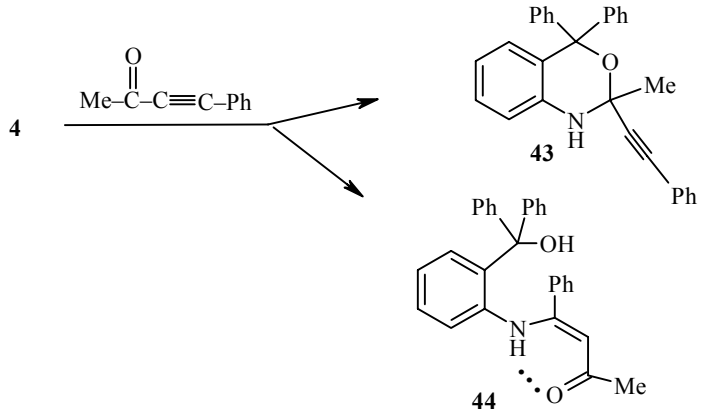
The reaction of the carbinols **4** with ketones and acetals is determined by the structure of the initial compounds. Thus, *o*-aminophenyldiphenylcarbinol **4a** only reacts with the simplest aliphatic ketones (acetone, methyl ethyl ketone, cyclohexanone) [26] and linear acetals **42** (with n = 2) [49] but does not enter into reaction with aromatic ketones or with ketones and acetals of branched structure [26, 49]. Under harsher reaction conditions (e.g., with increase in the temperature of the reaction mass to 60°C) there is only a side reaction with acylation of the carbinol **4a** by the acetic acid leading to the formation of 2-methyl-4,4-diphenyl-4H-3,1-benzoxazine (**33**) [26]:



R = Me; R^1 = Me, Et, β-(fur-2-yl)ethyl; R+R^1 = $(CH_2)_5$; R^2 = Me, Et

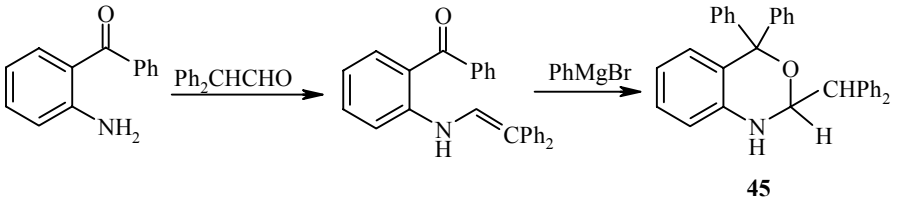
The experimental data indirectly confirm the mechanism of the reaction of the carbinols **4** with carbonyl compounds, which was established with the use of labeled atoms [48]. The initial stage of the reaction, i.e., attack by the amino group (carbinol) at the electrophilic carbon of the aldehyde, is realized by an S_N2 mechanism. The existence of steric hindrances in the case of the reaction of the carbinol **4a** with the acetals **42** (where n = 1, 0) and with ketones of complex structure prevents the occurrence of these reactions [49].

The carbinol **4a** is capable of entering into reaction with acetylphenylacetylene, containing an activated triple bond [51]. It was established that here, in addition to the formation of 2-methyl-2-phenylethynyl-4,4-diphenyl-1,4-dihydro-2H-3,1-benzoxazine **43**, the amino group of the carbinol **4** adds at the triple bond, leading to the aminovinyl ketone **44**. The yields of the products **43** and **44** amount to 55 and 25% respectively.

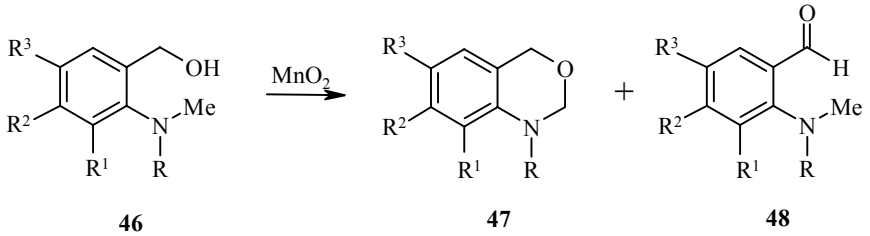


There are also a number of methods for the synthesis of 1,4-dihydro-2H-3,1-benzoxazines not having preparative significance [28, 34, 39, 52].

The heterocyclization of *o*-aminobenzyl alcohol involving unsaturated nitriles [28, 52] and the reduction of 4H-3,1-benzoxazines and their salts by organolithium and organomagnesium compounds are well known (see sections 1.2 and 1.3) [34]. 2-Diphenylmethyl-4,4-diphenyl-1,4-dihydro-2H-3,1-benzoxazine (**45**) was synthesized starting from *o*-aminobenzophenone [39].



Methods are known for the synthesis of N-alkyl-1,4-dihydro-2H-3,1-benzoxazines [53, 54]. The method proposed in [53] involves the oxidation of N,N-disubstituted 2-(hydroxymethyl)anilines **46**, leading to a mixture of the corresponding N-alkyldihydrobenzoxazines **47** and aldehydes **48**.



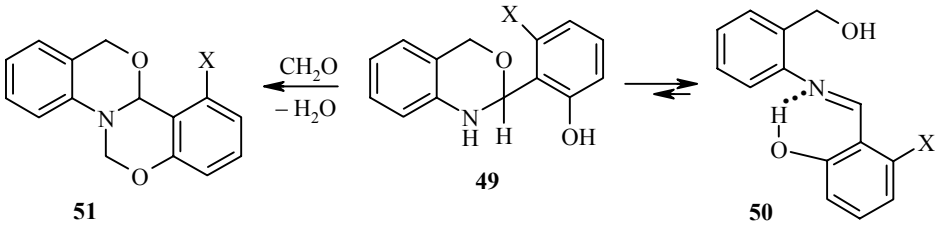
R = Me, Et; R^1, R^2, R^3 = H, Me, Cl

2.2. The Properties of 1,4-Dihydro-2H-3,1-benzoxazines

The distinctive nature of the reactivity of 1,4-dihydro-2H-3,1-benzoxazines is due to the fusion of the dihydro-1,3-oxazine ring with the benzene ring.

As already mentioned (see section 2.1), dihydrobenzoxazines not substituted at position 4 are capable of tautomeric transformation to the linear azomethine form (a Schiff base) [14, 45, 46, 55]. This tendency shows up most clearly in compounds whose alternative limiting structure is stabilized by an intramolecular hydrogen

bond [41, 55]. For example, for the 2-(*o*-hydroxyphenyl)-1,4-2H-3,1-benzoxazine (**49**) the tautomeric equilibrium with the corresponding salicylideneamine **50** is displaced toward the open form [55].

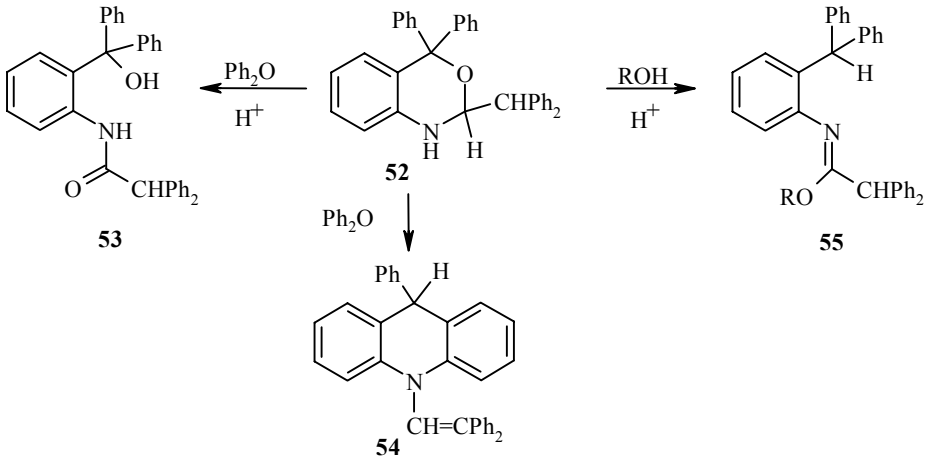


51 **49** **50**

X = H, Br

The reaction of the dihydrobenzoxazines **49** with formaldehyde gave the tetracyclic benzoxazines **51** [55, 56].

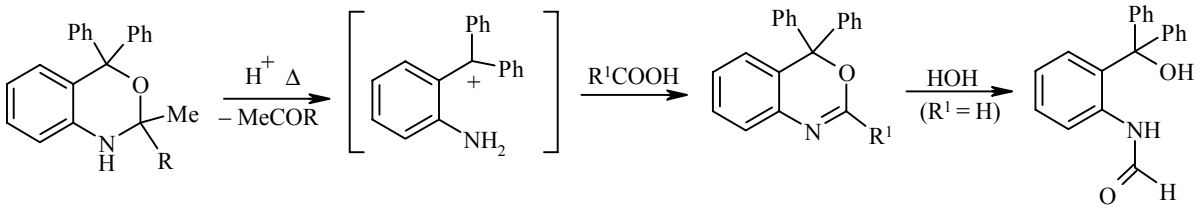
Under normal conditions 2,4-substituted 1,4-dihydro-2H-3,1-benzoxazines do not undergo tautomeric transformations [44]. Reactions with cleavage of the heterocycle have been described for a series of such structures [11, 26, 57, 58]. Thus, cleavage of the heterocycle to the anilide **53**, the acridane **54**, and the imidic ester **55**, depending on the experimental conditions, was studied in the case of 2-diphenylmethyl-4,4-diphenyl-1,4-dihydro-2H-3,1-benzoxazine (**52**) [11, 59].



53 **52** **55** **54**

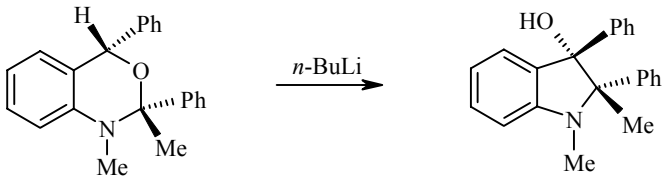
When heated in diphenyl ether in the presence of acids the dihydrobenzoxazine **52** forms the anilide **53**, while in the absence of the acid it forms the acridan **54**. Heating of the dihydrobenzoxazine **52** in alcohol ROH (R contains 5-8 carbon atoms) leads to the imidic ester **55**. The mechanisms of the transformations were discussed [11].

When the 2,4-substituted dihydrobenzoxazines are heated in organic acids, the heterocycle is broken and transformed with the formation of the corresponding 4H-3,1-benzoxazines [26, 27]. In an aqueous medium 4,4-diphenyl-4H-3,1-benzoxazine (R^1 = H) is hydrolyzed to (*o*-formylaminophenyl)carbinol [57]:



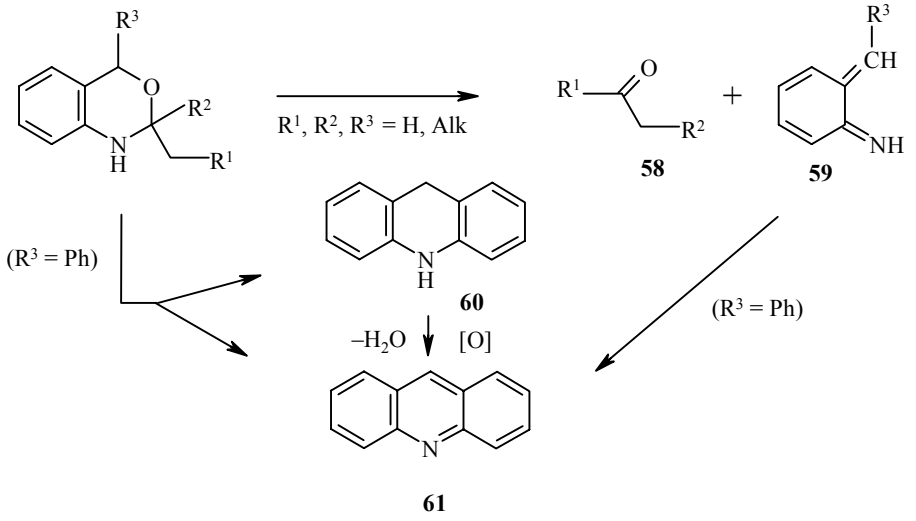
R = Me, Et; R^1 = H, Me

In strong bases 1,2-dimethyl-2,4-diphenyl-1,4-dihydro-2H-3,1-benzoxazine (**56**) undergoes a Wittig rearrangement with the formation of 3-hydroxyindoline **57** [34].



56 **57**

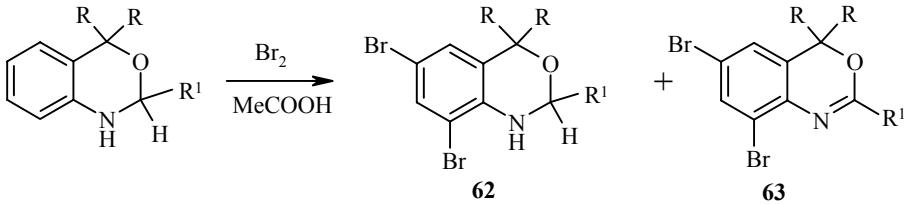
The thermal cleavage of the heterocycle in substituted 1,4-dihydro-2H-3,1-benzoxazines during pyrolysis has been described [58]. Either a Diels–Alder reaction with the formation of the ketones **58** and the azaxylylene **59** or recyclization, leading to the acridane **60** and acridine **61** [58, 11] with yields of ~8 and 47% respectively, can occur depending on the substituents at positions 2 and 4.



58 **59** **61**

Reactions with retention of the heterocycle include substitution in the aromatic and heterocyclic fragments.

Investigation of the bromination of 2,4-substituted 1,4-dihydro-2H-3,1-benzoxazines with a solution of bromine in acetic acid [60] showed that either the corresponding 6,8-dibromo-1,2-dihydrobenzoxazines **62** or the products from dehydrogenation of the latter, i.e., 6,8-dibromobenzoxazines **63**, are formed depending on the structure of the dihydrobenzoxazine and the concentration of the bromine.

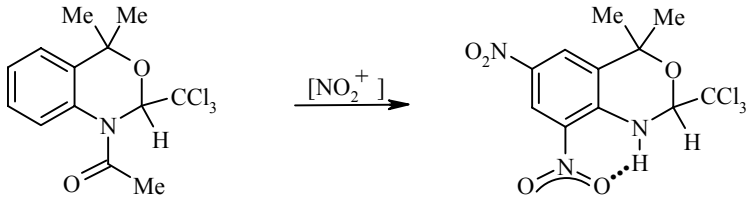


62 **63**

R = Alk, Ph; R1 = Alk, Ph, Fur

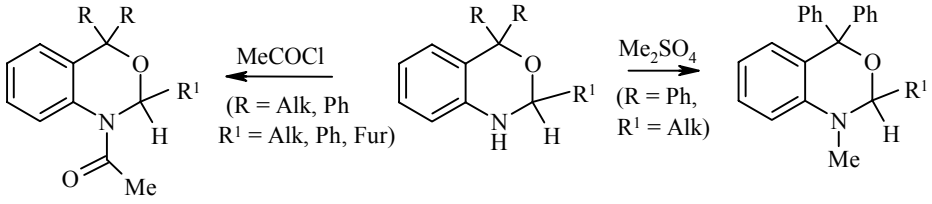
In the crystal of 6,8-dibromo-2-(5-nitro-2-furyl)-4,4-diphenyl-1,2-dihydro-2H-3,1-benzoxazine stacking interaction (overlap of the π-systems) was detected between the nitrofuran fragment of one molecule and the condensed benzene ring of another [60].

The nitration of dihydrobenzoxazines with a nitrating mixture leads to destruction of the heterocycle. Nitration of 1-acetyl-4,4-dimethyl-2-trichloromethyl-1,4-dihydro-2H-3,1-benzoxazine (**64**) leads to the substitution of two protons in the aromatic ring by nitro groups at the *ortho* and *para* positions in relation to the nitrogen; the acetyl group is not retained in the reaction product [61].

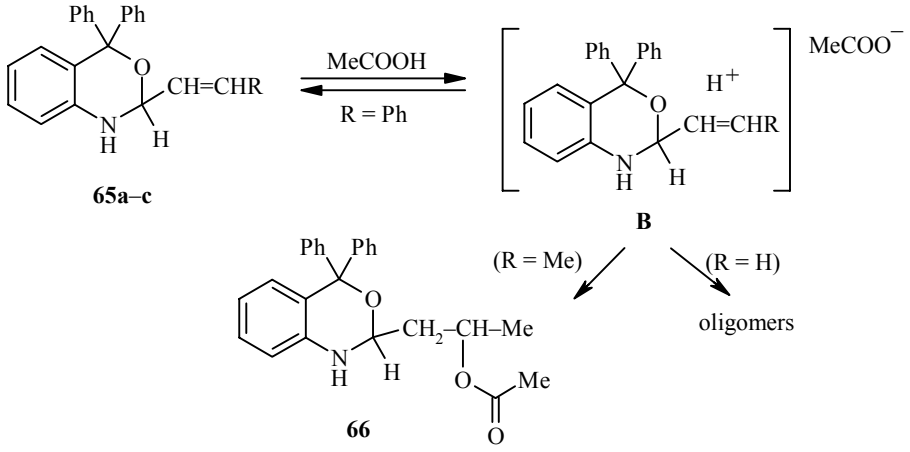


64

Substitution reactions in the heterocycle of 2,4-substituted dihydrobenzoxazines are represented by N-alkylation and N-acylation [62].



The reaction of the diphenyl-substituted *o*-aminobenzyl alcohol **4a** (see section 2.1) with unsaturated aldehydes leads to the formation of 1,4-dihydro-2H-3,1-benzoxazines **65**, the molecules of which contain a new reaction center – an exocyclic multiple bond [50]. Investigation of these products during their formation in acetic acid showed that the production of 2-vinyldihydrobenzoxazine **65a** is accompanied by cationic polymerization, while that of 2-(1-propenyl)dihydrobenzoxazine **65b** is accompanied by transformation into 2-(2-acetoxypropyl)-4,4-diphenyl-1,4-dihydro-2H-3,1-benzoxazine (**66**). The product **65c** does not undergo any transformations.



65a–c

B

66

65 a R = H, **b** R = Me, **c** R = Ph

The difference in the behavior of the dihydrobenzoxazines **65a-c** in acetic acid is determined by the nature of the substituent R and by the reactivity of the carbocation **B** [50].

3. THE SPECTRAL CHARACTERISTICS OF 4H-3,1-BENZOXAZINE DERIVATIVES

By using spectroscopic methods in the investigation of 4H-3,1-benzoxazine derivatives it is possible to determine their structure, including features of their stereochemical structure.

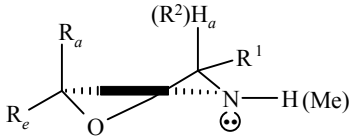
The IR spectra of 4H-3,1-benzoxazines are characterized by the presence of a strong band for the absorption of the C=N bond in the region of 1620-1635 cm^{-1} [14]. In the spectra of the benzoxazinium salts a hypsochromic shift of this band to 1650-1665 cm^{-1} is observed, indicating the presence of the $\bar{O}\text{–}\bar{C}\text{–}\bar{N}H^{+}$ fragment. In addition, the spectra of the salts also contain absorption bands for a quaternized nitrogen at 2550-2720 cm^{-1} and 1780-2350 cm^{-1} [14, 15].

The electronic spectra of 4H-3,1-benzoxazines are characterized by an absorption maximum in the region of 227-280 nm, due to the appearance of an oriented system of π–π conjugation between the aromatic ring and the C=N bond of the heterocycle [14].

Data from the ^{1}H NMR spectra of substituted 4H-3,1-benzoxazines support the idea of a planar structure for their molecules and equivalence between the geminal substituents at the $C_{(4)}$ atom of the heterocycle [15, 16].

A series of papers give the spectral characteristics and data on dissociation under electron impact for 2,4-substituted 1,4-dihydro-2H-3,1-benzoxazines [11, 26, 39, 41, 44, 46, 63-65]. The IR spectra of dihydrobenzoxazines contain a characteristic series of bands for the N–C–O fragment in the region of 1020-1180 cm^{-1} and also a band for the second amino group at 3350-3410 cm^{-1} [26]. The electronic spectra are close in the positions of the main absorption bands to the spectra of the initial amino alcohols [26, 39, 41, 63].

Analysis of the ^{1}H and ^{13}C NMR spectra shows that the heterocycle in 1,2,4-substituted 1,4-dihydro-2H-3,1-benzoxazines exists in a rigid half-chair conformation with a planar arrangement of the four atoms $C_{(4)}$–C=C–N and that the $C_{(2)}$–O groups deviate from this plane [44, 46].



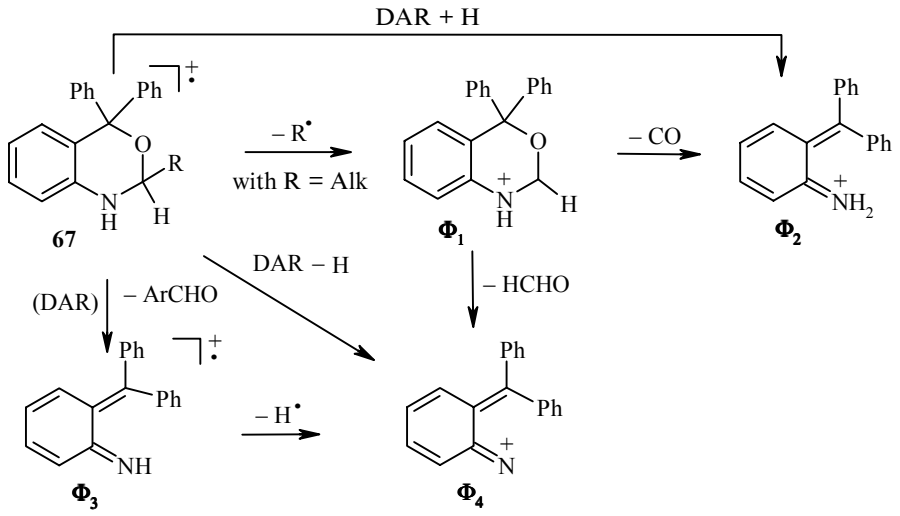
The presence of axial and equatorial isomers in relation to the position of the CH_3 group in a ratio of 75:25 was established for 4-methyl-1,4-dihydro-2H-3,1-benzoxazine. In its N-methyl derivative the ratio changes toward an increase in the content of the form with an equatorial 4-CH_3 substituent (up to 31%). In the case of *trans*-1,2,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazine the form with axial 2-CH_3 and equatorial 4-CH_3 substituents predominates in the mixture (57%) [46].

The nature of the ^{1}H NMR spectra of a series of 2,4,4-substituted dihydrobenzoxazines indicates the *cis* arrangement of the protons in the $NHC_{(2)}H_a$ fragment of the heterocycle [44].

Interconversion of the heterocycle of the *half-chair* ⇄ *half-chair* type becomes possible in the presence of geminal substituents at the $C_{(2)}$ and $C_{(4)}$ atoms of the heterocycle [44].

Substitution of the hydrogen at the nitrogen by an acyl group in dihydrobenzoxazines leads to a decrease in the basicity of the nitrogen, to weakening of the *p*–π interaction between the aromatic ring and the nitrogen atom of the heterocycle, and consequently to a decrease in the conformational rigidity of the molecule and the appearance of inversion of the heterocycle [62]. The presence of the N-methyl group in the molecule of 1,4-dihydro-2H-3,1-benzoxazines does not change the conformation of its heterocyclic fragment [62], and a different orientation of the N–CH_3 bond was proposed here [46].

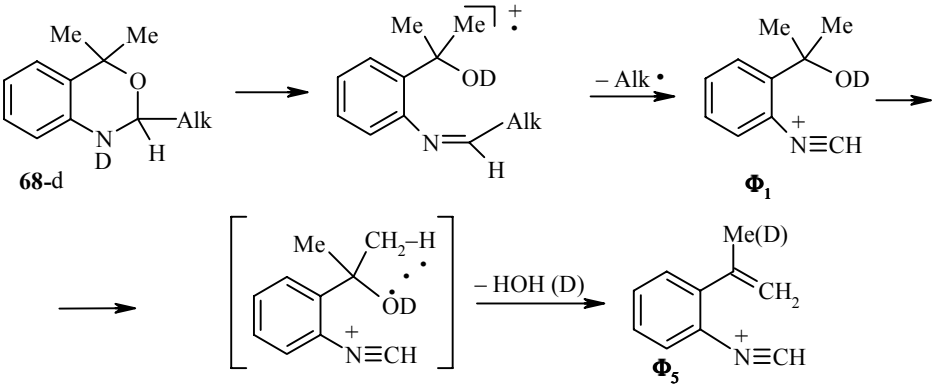
The mass spectra of dihydrobenzoxazines [44] contain singly charged molecular ions (M^{+}). The initial fragmentation of M^{+} in 4,4-diphenyl-1,4-dihydro-3,1-benzoxazines **67** is determined by the nature of the substituent at position 2.



In 2-alkyldihydrobenzoxazines the alkyl radicals are eliminated first with the formation of ions (Φ_1) with the structure of 4H-3,1-benzoxazines. For 2-aryldihydrobenzoxazines fragmentation begins with loss by the molecular ion of a molecule of aromatic aldehyde [a retro-Diels–Alder reaction (DAR)] [44, 64, 66]. The dissociation path with the formation of the Φ_4 cation is general (a DAR-H process) [66].

The formation of the Φ_1-Φ_4 ions confirms the existence of the cyclic form of the investigated compounds **67** in the gas phase [44, 66].

The fragmentation of M^+ in the dihydrobenzoxazines **68**, which have alkyl substituents in the heterocycle, obeys the general scheme. However, in addition to the peaks of M^+ and the Φ_1-Φ_4 ions the spectra also contain a peak for the Φ_5 ion, formed as a result of dehydration of the Φ_1 cation, as confirmed by investigations with a deuterium label [44].



This fact shows that unlike 4,4-diphenyldihydrobenzoxazines **67** 4,4-dimethyl-2-alkyldihydrobenzoxazines **68** can exist in an open-chain azomethine form in the gas phase [44].

THE BIOLOGICAL ACTIVITY OF DERIVATIVES OF THE 4H-3,1-BENZOXAZINE SERIES

From study of the patent literature on benzoxazines it can be concluded that a number of the compounds have clearly defined biological activity.

4H-3,1-Benzoxazines and their 1,2-dihydro derivatives in the form of bases and salts have been proposed as herbicides [67-70] and plant growth regulators [71-73]. Substituted 2-pyridyl-4H-3,1-benzoxazines [74] exhibit fungicidal activity.

There have been reports on the pharmacological activity of 4H-3,1-benzoxazine derivatives, exhibiting tranquillizing, analgesic, and spasmolytic activity [75, 76] and also sedative, hypnosedative, and antispasmodic activity [77-81] with very low toxicity [31].

Keto derivatives of 4H-3,1-benzoxazines have been proposed as medicinals [82, 83].

We hope that our brief review will assist all those interested in this promising class of heterocyclic compounds to reach decisions in the choice of targets and tasks for further investigations.

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