1,3-BENZOTHIAZINES (REVIEW)

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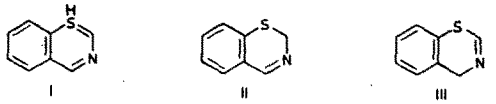
UDC 547.869.1

Data on the methods for the synthesis of 1,3-benzothiazines and their derivatives and their chemical properties and physiological activity are correlated.

1,3-Benzothiazine derivatives were described for the first time only in 1964 [1]; however, in connection with the chemical peculiarities of this class of heterocycles and in connection with the fact that numerous biologically active compounds have been found in the benzothiazine series, the research on this heterocyclic system has been undergoing extremely intensive development in the last decades.

Isomeric 1,3-benzothiazines I-III and their derivatives are examined in the present communication; data from research that has been abstracted in Chemical Abstracts up to 1972 inclusively are reflected in it.

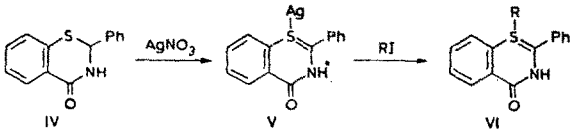


I II III

A previous review [2] also contains data relative to 1,3-benzothiazines, but only a few studies from recent years are discussed in it.

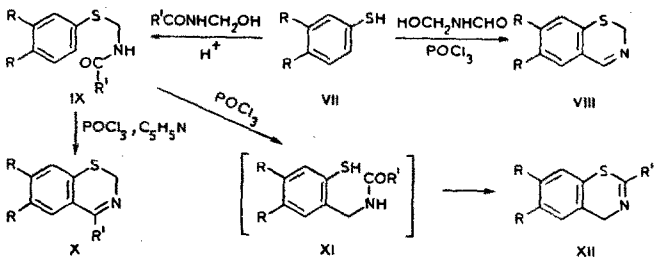
Methods for the Synthesis of 1,3-Benzothiazines

In the case of 1H-1,3-benzothiazines only substituted compounds of the VI type, obtained from dehydrobenzothiazinone IV through its silver derivative V, are known. Their structure was proved by hydrolysis, which leads to 2-(alkylthio)benzamides and benzaldehyde [3].



IV V VI

Derivative VIII, which does not contain substituents in the heteroring and is formed by condensation of N-(hydroxymethyl)formamide and 3,4-dimethoxythiophene (VII) in the presence of phosphorus oxychloride [4-6] is also known for 2H-1,3-benzothiazine (II) [4-6].



VII-XII R = OCH_3 ; R' = Ar, Alk, aralkyl

Other N-(hydroxymethyl)amides and VII form N-(arylthio)methylamides IX, which give 4-substituted benzothiazines X when they are heated with $POCl_3$ in pyridine [4, 7]. When pyridine is absent, the formation of a 1,3-benzothiazine from (arylthio)amides IX proceeds via two pathways to give 2H-1,3-benzothiazines X and 4H-1,3-benzothiazines XII [4, 11] as a result of rearrangement of (arylthio)methylamide IX to thiobenzylamide XI [8-10].

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 291-308, April, 1979. Original article submitted April 14, 1977; Revision submitted March 1, 1978.

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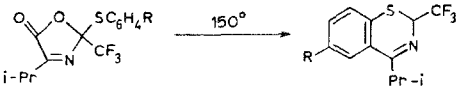
2H-1,3-Benzothiazine derivatives XIV were first obtained by thermolysis of 2-(arylthio)axazol-5-one XIII [12].

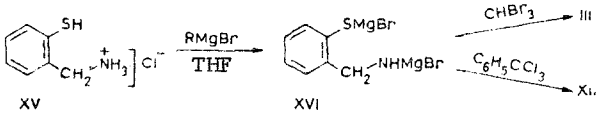


XIII XIV

XIII, XIV R = H, Me

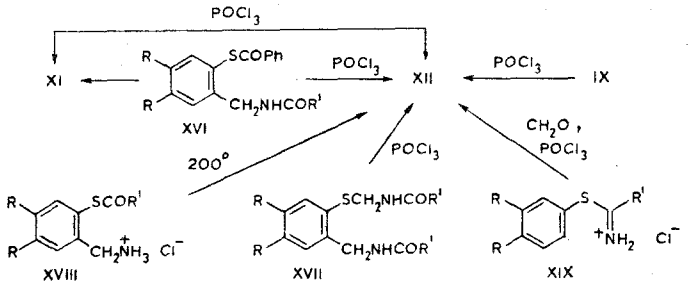
2-Oximino-4-methyl-2H-1,3-benzothiazine is formed in the reaction of 2-thiocyanatoacetophenone with hydroxylamine [13].

Unsubstituted 4H-1,3-benzothiazine (III) was synthesized by treatment of 2-mercaptobenzylamine hydrochloride (XV) with a Grignard reagent and subsequent heating of the resulting XVI with bromoform. The reaction of magnesium derivative XVI with benzotrichloride gives a benzothiazine of the XII type (R = H, R' = C_6H_5) [14, 15].



XV XVI

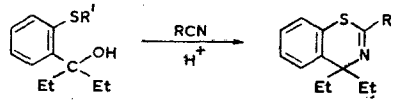
Prolonged heating of S-benzoyl-N-acyl-2-mercaptobenzylamine (XVI) with $POCl_3$ gives rise to 2-aryl- and 2-alkyl-4H-1,3-benzothiazine [8, 14-17]. Partial deacylation of the diacyl derivatives XXV gives amides which upon heating with condensing agents transforms to the 2-substituted compounds of type XII [8, 9, 18, 19].



R = H, OCH_3, OC_2H_5 ; R' = Ar, Alk, arakyl

Benzothiazines XII were also obtained by cyclization of XVII in the presence of phosphorus oxychloride [9]. As we pointed out above, N-(3,4-dialkoxyphenylthiomethyl)amides of the IX type (R = OCH_3, OC_2H_5) are converted to 4H-1,3-benzothiazines XII in the presence of acid condensing agents [5, 8, 18, 20]; intermolecular rearrangement of the amides precedes cyclization [9]. The corresponding benzothiazine XII is also formed when S-benzoyl-4,5-dimethoxy-2-mercaptobenzylamine hydrochloride (XVIII, R = OCH_3, R' = C_6H_5) is melted [21]. Aryl-substituted compounds of the XII type can also be obtained by cyclization of imino thio esters XIX with formaldehyde [22].

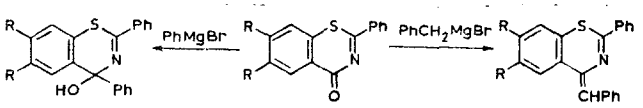
2,4,4-Trisubstituted 4H-1,3-benzothiazines XX are formed by the reaction of XXI and XXII with aliphatic and aromatic nitriles in the presence of mineral acids [23-25].



XXI, XXII XX

R = Me, Ph ; XXI R' = CH_2Ph ; XXII R' = H

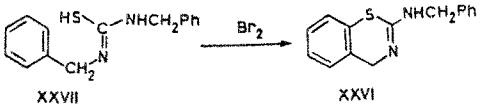
The formation of 2,4-substituted 4-hydroxy-4H-1,3-benzothiazines (XXIII, Ar = C_6H_5) is observed in the reaction of the corresponding oxo derivatives XXIV with phenylmagnesium bromide. 4-Benzylidene derivative XXV is formed in the case of benzylmagnesium bromide, probably through hydroxy compound XXIII [26, 27]



XXIII XXIV XXV

R = H, OMe

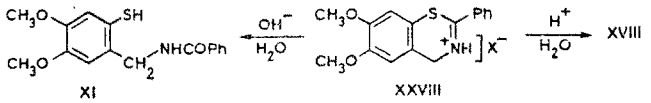
2-Benzylamino-4H-1,3-benzothiazine (XXVI) was synthesized by oxidation of N,N'-dibenzylthiourea (XXVII) with bromine [28].



XXVII XXVI

Chemical Properties of 4H- and 2 H-1,3-Benzothiazines

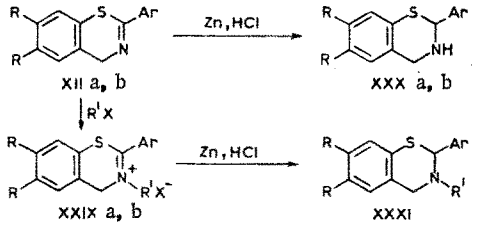
Heteroring-substituted 4H-1,3-benzothiazines are bases and react with acids to give the corresponding salts XXVIII, which are readily hydrolyzed to give amine salts of the XVIII type. 4H-1,3-Benzothiazines are stable in the presence of alkalis; however, the heteroring is opened at the C–S bond to give an N-benzoyl derivative of the XI type under severe conditions [21].



XI XXVIII XVIII

4H-1,3-Benzothiazines XII (R = C_6H_5) react with alkyl halides to give quaternary salts (XXIX) [29, 30]. Benzothiazines XII and their salts (XXIX) are reduced to 2,3-dihydro derivatives with zinc in the presence of acids; however, they could not be reduced with complex hydrides [31].

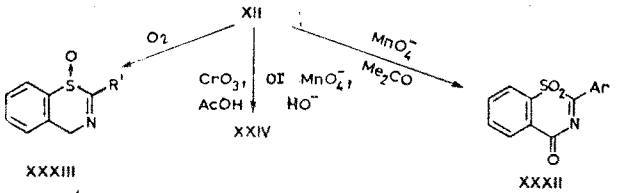
The oxidation of 2-aryl-6,7-dialkoxy derivatives XII (R = OAlk, R' = Ar) leads to 4-oxobenzothiazines of the XXIV type [5, 32], while derivatives that do not have alkoxy groups are oxidized to 4-oxo compounds only by permanganate in alkaline media [33]. The oxidation of benzothiazine XII



XII a, b XXX a, b XXIX a, b XXXI

a R=H ; b R=OMe, OEt ; Ar = Ph; 3,4-$(CH_3O)_2C_6H_3$; 4-CH_3OOC-C_6H_4

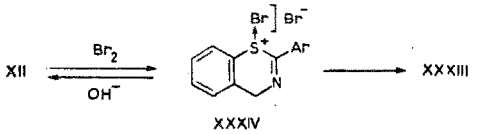
(R = H, R' = Ar) with permanganate in acetone leads to the formation of 4-oxo 1,1-dioxide XXXII [33]. 2-Alkyl-1,3-benzothiazines of the XII type are oxidized by air oxygen to give sulfoxides XXXIII [33, 34]. This sort of oxidation is not observed in the case of 2-aryl-substituted compounds [33].



XXXIII XXXII

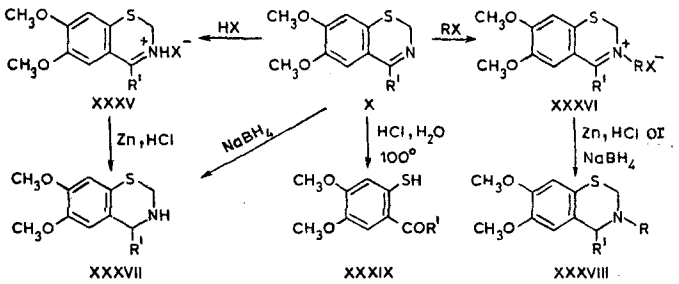
XXXIII R' = Alk

The reaction of compounds of the XII type with bromine leads to 1,1-dibromide XXXIV, which is converted to the starting compound (instead of the expected oxide XXXIII) when it is treated with alkali. However, dibromide XXXIV forms sulfoxide XXXIII (R' = Ar) when it is heated in propyl alcohol [33].



XXXIV

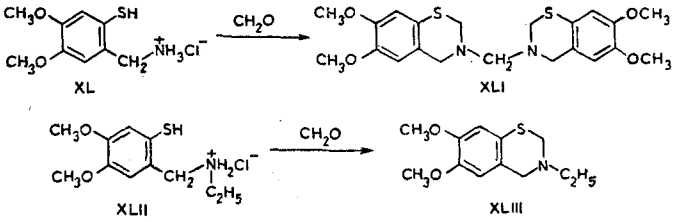
Little study has been devoted to the properties of 2H-1,3-benzothiazines of the II type. Like the 4H isomers, they form salts XXXV [4, 12] with mineral acids and quaternary salts XXXVI with alkyl or aralkyl halides [4]. Salts XXXV and XXXVI are reduced to dihydro derivatives XXXVII and XXXVIII by zinc in acid or sodium borohydride in alkaline media [4]. Their acid hydrolysis leads to mercapto derivatives XXXIX [4, 12].



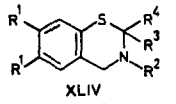
3,4-Dihydro-2H-1,3-benzothiazines

The names 3,4-dihydro-2H- or 2,3-dihydro-4H-1,3-benzothiazines for dihydro-1,3-benzothiazines are equally prevalent in the literature. In conformity with the IUPAC nomenclature, we will use the first of these names.

Attempts to synthesize compounds of the XXXVII type, which do not have a substituent in the heteroring, have thus far been unsuccessful. The condensation of salt XL with formaldehyde leads to the formation of methylene-bis-3,4-dihydro derivative XLI [35]. Similar condensation of N-ethyl-substituted salt XLII and formaldehyde gives N-ethyldihydro derivative XLIII [35].



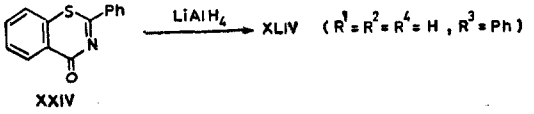
The generally accepted method for the synthesis of dihydro-1,3-benzothiazines XLIV is condensation of 2-mercaptobenzylamines XV, XL, and XLII with aldehydes and ketones [35].



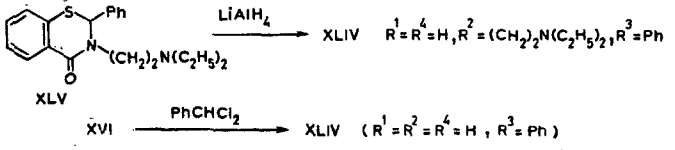
XLIV

$R^1 = H, OCH_3$; R^3 = alkyl, aryl; R^4 = H, alkyl, cycloalkyl ,

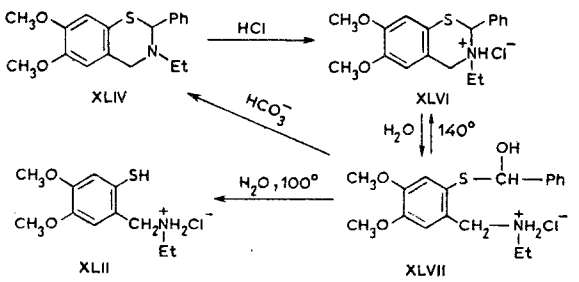
The above-mentioned reduction of 4H-1,3-benzothiazine derivatives XII or their quaternary salts (XXIX) has been used in the synthesis of only a few dihydro derivatives [31]. It should be noted that the reduction of 4-oxobenzothiazines XXIV (R = H, Ar = C_6H_5) to dihydro derivatives XLIV has been described; however, this method is not always successful [35-37]. Compound XVI is converted to the same derivative XLIV on reaction with benzal chloride [38].



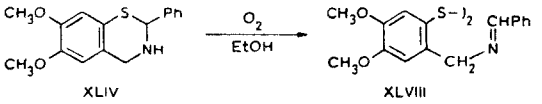
The reduction of the oxo group in 4-oxodihydrobenzothiazine LV leads to dihydrobenzothiazine XLIV [39].



3,4-Dihydro-2H-1,3-benzothiazines form salts XLVI, which are quite soluble in water and are readily hydrolyzed to the corresponding 2-mercaptobenzylamines XIII through thio hemiacetal XLVII, hydrochloride XLVI is formed from it by the loss of a molecule of water when it is melted. A benzothiazine ring is reformed when an aqueous solution of XLVII is neutralized [5].

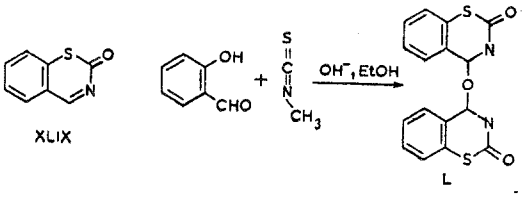


Dihydro derivative XLIVd is oxidized by air oxygen in alcohol solution to give disulfide XLVIII [5].



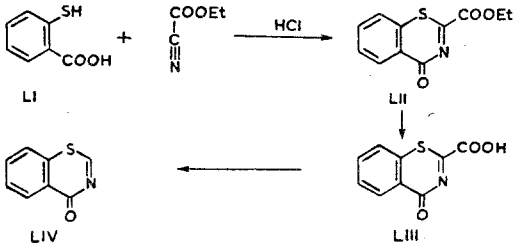
Oxo Derivatives of 1,3-Benzothiazines

2-Oxo-4H-1,3-benzothiazine (XLIX) has not been described. Only its dihydro derivative (L) was obtained by reaction of salicylaldehyde with methyl isocyanate [40].

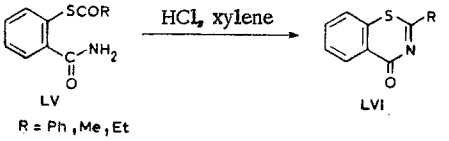


4-Oxo-4H-1,3-benzothiazine (LIV) is synthesized through 2-carbethoxy derivative LII, obtained from 2-mercaptobenzoic acid (LI) and ethyl cyanoformate. Hydrolysis gives acid LIII, the decarboxylation of which gives LIV [42].

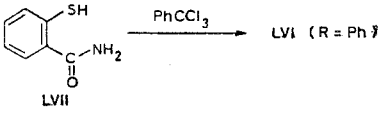
As we pointed out above, the oxidation of 2-aryl-4H-1,3-benzothiazines (XII) leads to 4-oxo derivatives [32, 33].



The cyclization of 2-(acylmercapto)benzamides LV in the presence of hydrogen chloride is a general method for the preparation of 4-oxo derivatives LVI [43]. This method was also used to synthesize 6,7-dialkoxy derivatives of the LVI type [32].

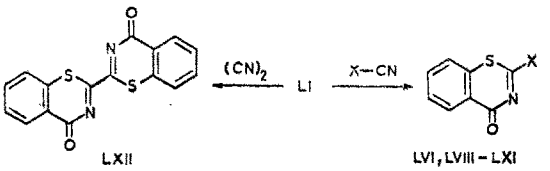


2-Phenyl-4-oxo-4H-1,3-benzothiazine (LVI, R = C_6H_5) is formed when 2-mercaptobenzamide (LVII) is treated with benzotrichloride [44].



The condensation of 2-mercaptobenzoic acid (LI) with various cyano derivatives is a universal method for the synthesis of 2-substituted 4-oxo-4H-1,3-benzothiazines. Thus acid LI (as well as substituted acids) reacts with aromatic nitriles to give 2-aryl-4-oxo derivatives LVI (R = Ar) [45], with cyanoacetic esters to give 2-(carbethoxymethyl) derivatives LVIII [42], with chloroacetonitrile to give chloromethyl-substituted

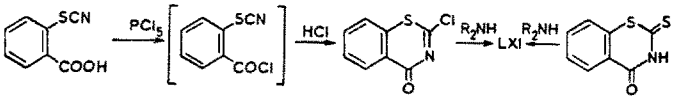
compounds LIX [42], with cyanourea to give ureido derivatives LX [46], with N,N-disubstituted cyanamides to give compounds of the LXI type [47], and with cyanogen to give 2,2'-bis(1,3-benzothiazinyl) derivative LXII [48, 49].



LXII LVI, LVIII – LXI

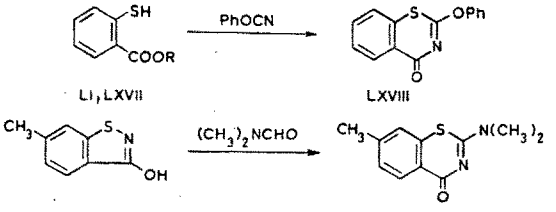
LVI X=Ar ; LVIII X=CH_2COOEt ; LIX X=CH_2Cl ; LX X=$NHCONH_2$; LXI X=NR_2

The reaction of 2-thiocyanatobenzoic acid (LXIII) with PCl_5 leads to 2-chloro-4-oxo-4H-1,3-benzothiazine (LXIV). Ring closing can also be accomplished by treatment of intermediate acid chloride LXV with hydrogen chloride [50, 51]. Reactive chloro derivative LXIV readily gives amines LXI, which are also formed in the reaction of 2-thioxo-4-oxo-1,3-benzothiazine (LXVI) with amines [51, 52].



LXIII LXV LXIV LXVI

2-Phenoxy-4-oxo-1,3-benzothiazine (LXVIII) is obtained as a result of condensation of 2-mercaptobenzoic acid (LI) or its methyl ester (LXVII) and phenyl cyanate [53, 54]. The reaction of 3-hydroxy-1,2-benzothiazole LXIX and dimethylformamide (DMF) leads to the formation of 2-dimethylamino derivative LXX [55].

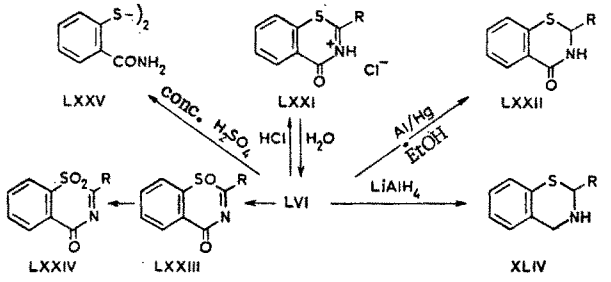


LI, LXVII LXVIII

LXIX LXX

LI R=H ; LXVII R=CH_3

4-Oxobenzothiazines LVI are weak bases. They form salts LXXI only in nonaqueous media. 4-Oxodihydro derivatives LXXII were obtained by their reduction with aluminum amalgam [31, 43]. The problem of the reduction of compounds of the LVI type with lithium aluminum hydride cannot yet be regarded as completely solved [31, 36, 37].



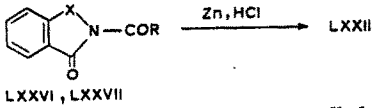
LXXV LXXI LXXII

LXXIV LXXIII LVI XLIV

4-Oxobenzothiazines LVI also undergo reactions involving the carbonyl group: oximes are formed with hydroxylamine [45], and 4-hydroxybenzothiazines XXIII are formed with Grignard reagents [26, 27] (see above). They are oxidized successively by peracetic acid to sulfoxides LXXIII and sulfones LXXIV [5]. Oxidation with permanganate also leads to sulfones [33].

The acid hydrolysis of 4-oxobenzothiazine LVI gives diamide LXXV [44].

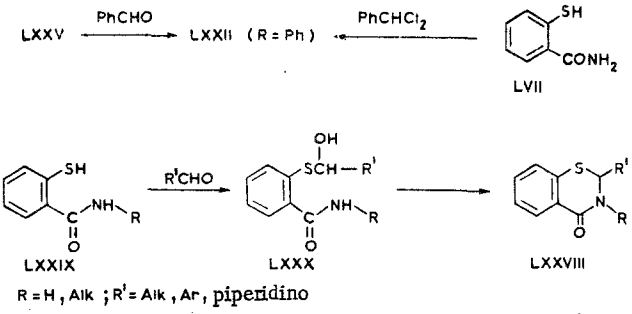
4-Oxo-2,3-dihydro-4H-1,3-benzothiazine itself (LXXII, R = H) is unknown, but a number of good methods have been developed for the synthesis of its 2-mono- and 2,3-disubstituted derivatives. 2-Alkyl- and 2-aralkyl-4-oxo-2,3-dihydro-4H-1,3-benzothiazines (LXXII) were first obtained by reduction of N-acylbenzisothiazolones (LXXVI) or their 1-oxides (LXXVII) with zinc in the presence of an acid [1].



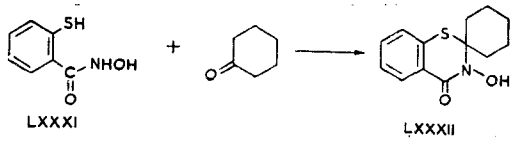
LXXVI, LXXVII

LXXVI X=S ; LXXVII X=SO ; R=Alk, aralkyl

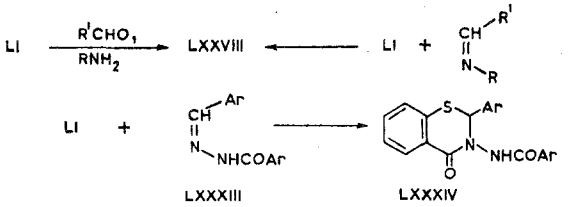
This method was found to be unsuitable for the synthesis of 2-aryl derivatives [1]. At the same time, a derivative of the LXXII type (R = C_6H_5) is obtained when diamide LXXV is heated with excess benzaldehyde [1]. The latter reaction is the basis for a general method for the preparation of oxobenzothiazones by condensation of 2-mercaptobenzamides LXXIX with aldehydes and ketones [56-62]. The cyclization proceeds through intermediate thio hemiacetal LXXX [58].



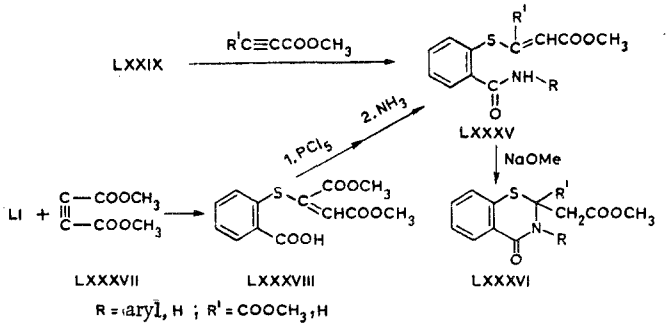
Hydroxy derivative LXXII (R = C_6H_5) [63] is formed when 2-mercaptobenzamide (LVII) and benzal chloride are heated in piperidine. The condensation of hydroxamic acid LXXXI and cyclohexanone gives 3-hydroxy-4-oxobenzothiazine LXXXII [64].



The reaction of 2-mercaptobenzoic acid (LI) with aldehydes and primary amines leads – through the Schiff base – to 2,3-disubstituted 4-oxo derivative LXXVIII [38, 65-70]. 3-Acylamino derivative LXXXIV was obtained by the same method from acid LI and N-acylhydrazones LXXXIII [71].

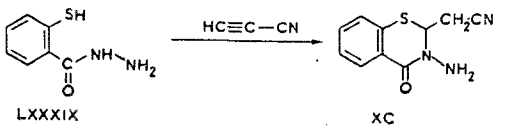


Vinyl sulfide LXXXV, which is formed by the addition of N-alkyl-2-mercaptobenzamide (LXXIX) to dimethyl acetylenedicarboxylate, undergoes cyclization to 4-oxodihydrobenzothiazine LXXXVI in the presence of sodium methoxide [72].

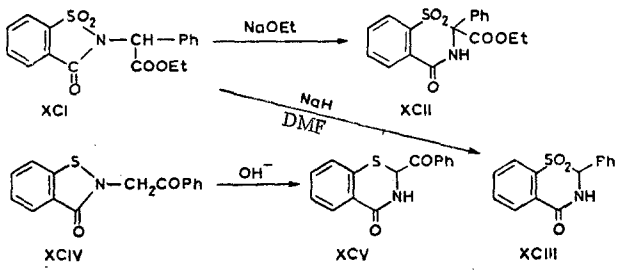


The reaction of acid LI with dimethyl acetylenedicarboxylate (LXXXVII) gives vinyl sulfide LXXXVIII, which is also converted to benzothiazine LXXXVI through the acid chloride and amide LXXXV.

The reaction of thiosalicylic acid hydrazide LXXXIX with propiolic acid nitrile gives 3-amino-2-cyanomethyl-4-oxobenzothiazine (XC) in almost quantitative yield [48].

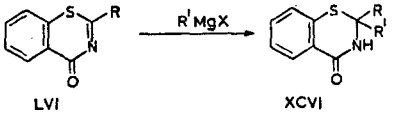


Treatment of saccharin derivative XCI with sodium ethoxide leads to ring expansion with the formation of 2,2-disubstituted benzothiazine XCII, while treatment with sodium hydride in DMF leads to the corresponding 2-phenyl-substituted XCIII [60].

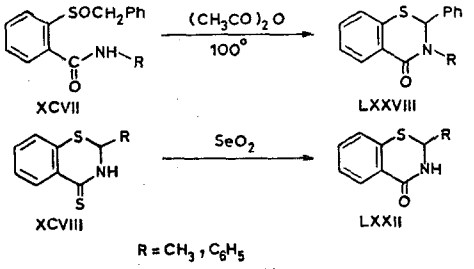


2-Phenacyl-1,2-benzisothiazolin-3-one (XCIV) also undergoes ring expansion under the influence of alkalis and is converted to 2-benzoyl derivative XCV [62].

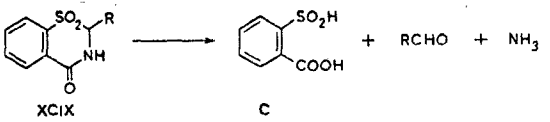
4-Oxodihydrobenzothiazines LXXII and XCVI are formed in the reduction of 4-oxobenzothiazines (LVI) with lithium aluminum hydride [31, 43] and, correspondingly, as a result of the addition of alkylmagnesium halides to the C=N bond [26, 27].



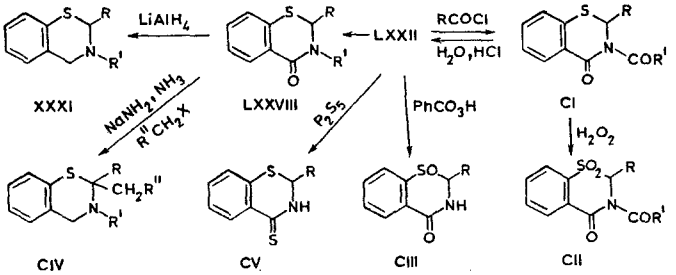
An oxo derivative of the LXXVIII type is formed when sulfoxide XCVII is heated with acetic anhydride [73]. The oxidation of 4-thioxobenzothiazine XCVIII to oxo compound LXXII with selenium dioxide has also been described [63].



Chemical Properties of 4-Oxo-2,3-dihydro-4H-1,3-benzothiazines. The alkaline hydrolysis of 4-oxodihydro derivatives LXXII leads to 2-mercaptobenzoic acid (LI), the corresponding aldehyde, and ammonia [1]. However, 2-carboxybenzenesulfinic acid (C) is formed along with the aldehyde and ammonia from sulfone XCIX [43, 56, 60].

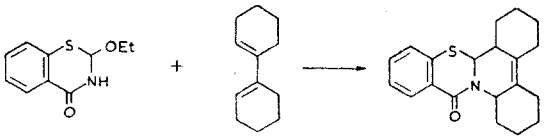


2,3-Dihydrobenzothiazines LXXII, which do not have substituents attached to the nitrogen atom, are converted by reaction with acid chlorides in the presence of pyridine to N-acyl derivatives CI, which are readily hydrolyzed to give the starting compounds [1].



Hydrogen peroxide [1, 60, 72] and peracetic acid [56, 57, 74] oxidize 4-oxodihydrobenzothiazines LXXII to 1,1-dioxide CII; N-acyl derivatives are also oxidized by hydrogen peroxide [1]. Perbenzoic acid can be used for the selective oxidation to sulfoxides CIII [74], whereas a mixture of the sulfoxide and sulfone [72] or only the sulfone [65] is formed in the case of potassium permanganate. Compounds LXXII form N-alkyl-substituted LXXVIII with alkylating reagents [57, 58, 60].

For the preparation of 2,2-disubstituted CIV monosubstituted compounds LXXVIII are alkylated in the presence of alkali metal amides in liquid ammonia [68, 70, 75]. Compounds of the LXXVIII type are reduced to hydrobenzothiazines XXXI by lithium aluminum hydride [38]. The corresponding 4-thiones CV can be obtained from 4-oxodihydrobenzothiazines LXXII and phosphorus pentasulfide [63]. Dihydro derivatives of the CVI type and conjugated dienes such as 1,1'-dicyclohexenyl form Diels–Alder adducts (CVII) [41].



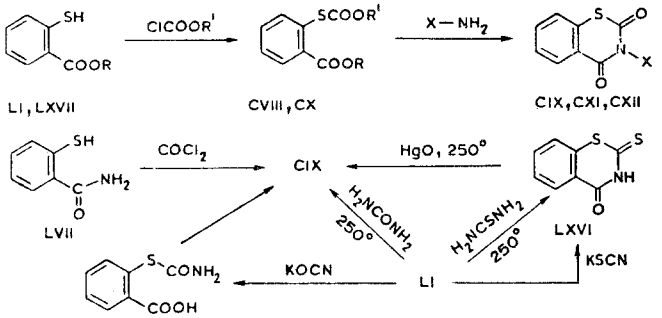
CVI CVII

2,4-Dioxo-1,3-benzothiazines and Their Sulfur Analogs and Imines

Judging from the number of publications devoted to these derivatives of benzo-1,3-thiazine, they are of a great deal of interest to researchers. Their synthesis is usually based on the use of 2-mercaptobenzoic acid (LI) or its derivative as the starting reagent.

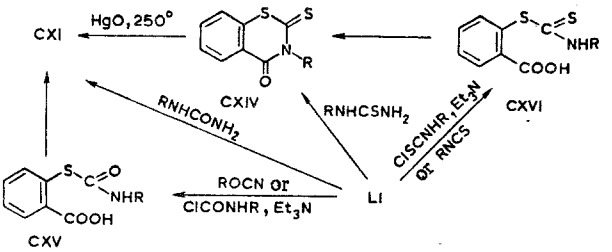
Thus acid LI and ethyl chloroformate form intermediate CVIII, which reacts with ammonia to give 2,4-dioxo-1,3-benzothiazine (CIX) [76, 77]. Methyl 2-mercaptobenzoate (LXVII) also reacts similarly with ethyl chloroformate to give CX, which undergoes cyclization when it is treated with ammonia [76]. The reaction of CVIII with primary amines leads to 3-substituted dioxo derivatives CXI [77], and the reaction with hydrazine hydrate leads to 3-amino derivatives CXII [77].

Dioxobenzothiazine CIX can also be obtained by cyclization of 2-mercaptobenzamide (LVII) with phosgene [76, 77]. The reaction of acid LI and potassium cyanate leads to carbamic acid derivative CXIII, heating of which with thionyl chloride, hydrochloric acid, or p-toluenesulfonic acid give benzothiazine CIX [76, 78]. 2,4-Dioxo derivative CIX is also formed by fusion of acid LI with urea, and 2-thioxo-4-oxo derivative LXVI is formed with thiourea [46, 79]. Derivative LXVI is also obtained from 2-mercaptobenzoic acid and potassium thiocyanate; it is converted to 2,4-dioxo derivative CIX when it is heated for a long time with mercuric oxide or lead(II) [77].



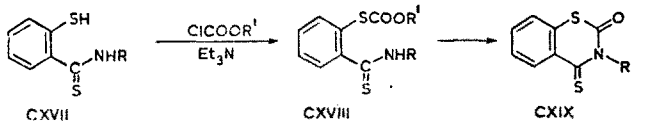
LI, CVIII R=H ; LXVII, CX R=CH_3 ; CIX X=H ; CXI X=R ; CXII X=NH_2

Dioxo derivatives CXI are formed by fusion of LI and N-alkylureas, and 2-thioxo derivatives CXIV are formed by fusion with thioureas under similar conditions [80]. For the preparation of 3-substituted dioxo derivatives CXI the product of the reaction of acid LI and isocyanate or chloride of carbamic acid – carbamic acid derivative CXV – was heated with thionyl chloride [76, 78, 81, 82]. The reaction of LI with isothiocyanates or chlorides of thiocarbamic acids gives thiocarbamic acid derivative CXVI, which, as in the preceding case, undergoes cyclization to benzothiazine CXIV. 2,4-Dioxo derivatives CXI can be obtained by heating CXIV with mercuric oxide [81-84].



The reaction of 2-mercaptobenzamide CXVII and chloroformic acid esters serves for the preparation of

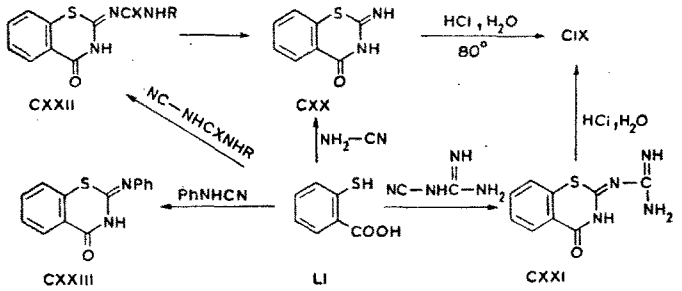
4-thioxo-2-oxobenzothiazine CXIX through intermediate CXVIII [85-87].



CXVII CXVIII CXIX

R = Alk, Ar

The condensation of 2-mercaptobenzoic acid (LI) with cyanamide leads to imine CXX, the hydrolysis of which with hydrochloric acid gives 2,4-dioxo derivative CIX [76, 88, 89]. The reaction of LI with cyanoguanidine leads to 2-guanidino derivative CXXI, the hydrolysis of which takes place with the formation of CIX [89].

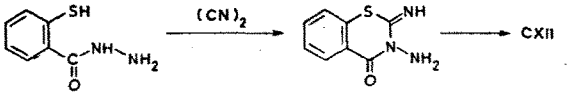


CXXII CXX CIX CXXIII LI CXXI

CXXII R = H, Alk, Ar, X = O, S

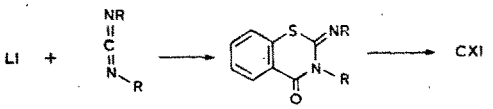
2-Ureidobenzothiazines CXXII are formed in the reaction of cyanourea, cyanothiourea, and their derivatives with acid LI, whereas 2,4-dioxo derivative CIX is formed under more severe conditions [90, 91]. Acid LI and phenylcyanamide form 2-phenylimino-4-oxo-1,3-benzothiazine (CXXIII) [87].

The condensation of hydrazide LXXXIX with cyanogen leads to 2-imino-3-amino derivative CXXIV, the hydrolysis of which gives 3-amino-2,4-dioxo-1,3-benzothiazine (CXII) [48, 92].



LXXXIX CXXIV CXII

The acid hydrolysis of the product (CXXIV) of condensation of acid LI with carbodiimides CXXV serves as a method for the synthesis of N-substituted 2,4-dioxobenzotriazines CXI [93, 94].

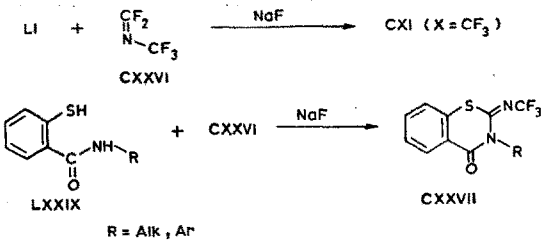


CXXV CXXIV CXI

R = Alk, cyclohexyl, aralkyl, Ar

As we mentioned above, the reaction of 2-thiocyanatobenzoic acid and phosphorus pentachloride gives 2-chloro-4-oxo-4H-1,3-benzothiazine (LXIII), the hydrolysis of which leads to 2,4-dioxo derivative CIX [51].

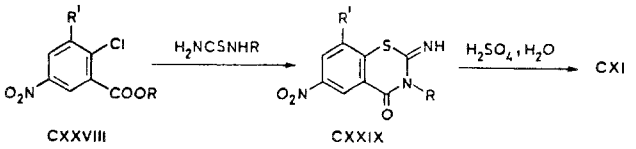
A 3-trifluoromethyl-2,4-dioxo derivative of the CXI type (X = CF_3) is formed as a result of the reaction of perfluoro-2-azapropene (CXXVI) with acid LI [95], whereas 2-trifluoromethylamino-4-oxo derivatives CXXVII are formed as a result of the reaction with N-substituted 2-mercaptobenzamides (LXXIX) [96].



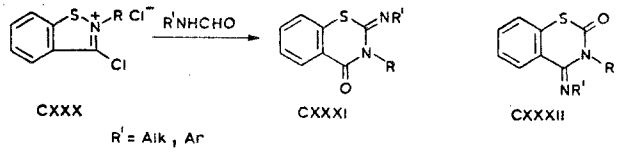
CXXVI LXXIX CXXVII

R = Alk, Ar

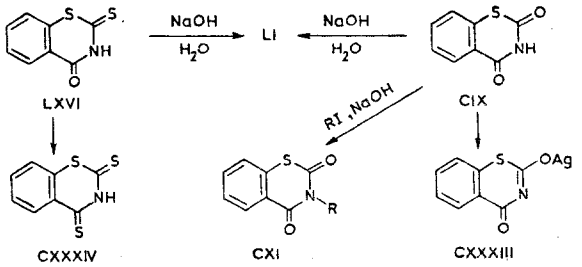
A suitable method for the synthesis of 2,4-dioxo derivatives CXI is hydrolysis of the corresponding imines CXXIX, which are formed from a substituted thiourea and 2-chloro-5-nitrobenzoic acid esters (CXXVIII) [97].



The reaction of 2-alkyl-3-chloro-1,2-benzothiazolium chlorides (CXXX) and substituted formamides gave 2- and 4-imino derivatives of dioxobenzothiazines (CXXXI, CXXXII) [98].



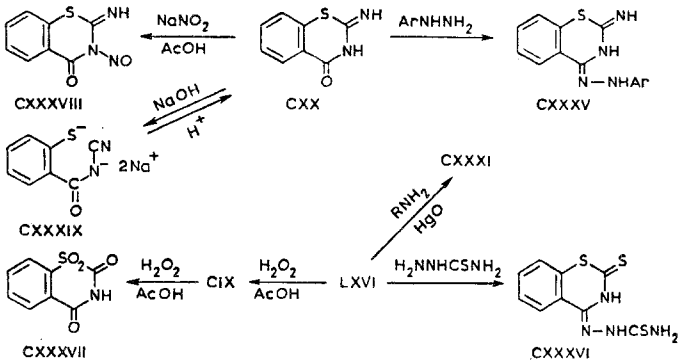
Chemical Properties of 2,4-Dioxo-1,3-benzothiazines and Their Sulfur Analogs and Imines. The alkaline hydrolysis of 2,4-dioxo- and 2-thioxo-4-oxobenzothiazines CIX and LXVI leads to the formation of 2-mercaptobenzoic acid (LI) [79]. Compound CIX reacts with alkali to give a salt, which is converted to silver salt CXXXIII when it is treated with silver nitrate [89]. The alkylation of dioxobenzothiazines CIX with alkyl iodides takes place with the formation of 3-alkyl-substituted CXI [76, 77, 79, 89].



Methyl ester LXVII and phenyl isothiocyanate are formed by cleavage of 3-phenyl-2-thioxo-4-oxo-1,3-benzothiazine (CXIV, R = C_6H_5) with potassium hydroxide in methanol, whereas acid LI itself and phenyl isothiocyanate are formed in acetone [99].

The benzolation of CIX and LXVI leads to N-benzoyl derivatives [79].

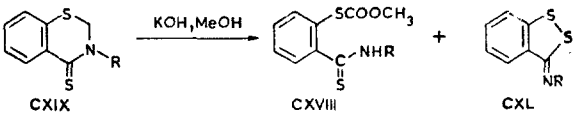
The characteristic reactions of the carbonyl groups were observed in the case of 2-imino-4-oxo-1,3-benzothiazine (CXX) during the formation of its phenylhydrazone (CXXXV) [89] and in the case of the 2-thioxo-4-oxo derivative during the formation of the thiosemicarbazone (CXXXVI) [84].



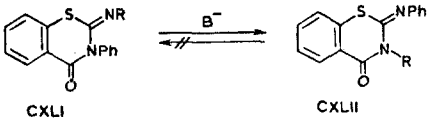
Brief treatment of 2-thioxo derivative LXVI with hydrogen peroxide in acetic acid converts LXVI to 2,4-dioxo compound CIX, and further oxidation to sulfone CXXXVII occurs in the case of prolonged treatment [46, 84]. The reaction of 2-thione LXVI with mercuric oxide and methylamine gives 2-methylimino-4-oxo derivative CXXXI (R = H, R' = CH_3) [52, 87, 100, 101].

The reaction of 2-imino-4-oxo compound CXX and sodium nitrite in acetic acid leads to the formation of 3-nitroderivative CXXXVIII [89]. When the imino oxo derivative is heated in 10% sodium hydroxide solutions, the ring undergoes reversible opening to give salt CXXXIX [102].

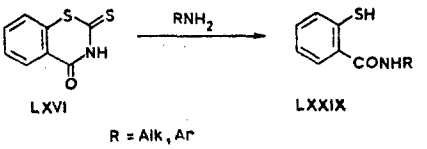
3-Phenyl-2-oxo-4-thioxo-1,3-benzothiazine (CXIX, R = C_6H_5) is also cleaved by potassium hydroxide in methanol to give a thiobenzanilide derivative (CXVIII) and CXL [99].



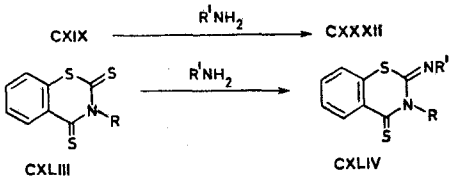
The alkaline opening of the ring of 2-imino- and 4-imino derivatives [103] and the Dimroth rearrangement of 3-phenyl-2-alkylimino-4-oxo-1,3-benzothiazine (CXLI) to CXLII in the presence of a base [52] have also been described.



2-Thioxo-4-oxo derivative LXVI is cleaved in the presence of primary amines to give 2-mercaptobenzamides LXXIX [46, 104, 105].



2-Oxo-4-thioxo-1,3-benzothiazines (CXIX) react with primary amines give 4-imino derivatives CXXXII, whereas 2,4-dithioxo derivatives CXLIII are converted to 2-imines CXLIV under similar conditions [52].



The reaction of 2,4-dioxo-2-thioxo-4-oxo-1,3-benzothiazines with carboxylic acid amides leads to the formation of 4-quinazolone derivatives [106, 107]. Compound CXL and isothiocyanate were obtained as a result of alkaline opening of dithione CXLIII [85].

Biological Activity. The biological activity of 1,3-benzothiazine derivatives is diversified. Antidepressants [70, 75, 108], psychostimulators [68, 92], tranquilizers [67, 92], analgetics [47, 61], bacteriostats [77], fungistats [77], fungicides [95, 109], and substances that have spasmolytic [5, 110-112], antipyretic [77], sedative [61], and antiphlogistic [77] properties are found among them.

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