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1,2-BENZISOTHIAZOL-3(2H)-ONESAND HETEROCYCLIC ANNELATED ISOTHIAZOL-3(2H)-ONES, PART 11: SYNTHESIS, REACTIONS, AND BIOLOGICAL ACTIVITY

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1,2-BENZISOTHIAZOL-3(2*H*)-ONES AND HETEROCYCLIC ANNELATED ISOTHIAZOL-3(2*H*)-ONES, PART II: SYNTHESIS, REACTIONS, AND BIOLOGICAL ACTIVITY

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This review covers the synthesis, reactions, and biological activity of heterocyclic annelated isothiazol-3(2*H*)-ones and a new series of 1,2-benzisothiazol-3(2*H*)-ones of the last ten years. Isothiazolo[5,4-*b*]pyridine-3(2*H*)-ones have been reported by oxidative cyclization of 2-mercapto-3-pyridinecarboxamides, 2,2′-dithio- and 2,2′-trithiobis(3-pyridinecarboxamides) and by cyclocondensation of 2-thiosubstituted 3-pyridinecarboxamides. The isomeric isothiazolopyridine-3(2*H*)-ones, pyrimidine-3(2*H*)-ones and the thienoisothiazol-3(2*H*)-ones have been described. 1,2-Benzisothiazol-3(2*H*)-ones and their heterocyclic bioisosteric derivatives have been reported to possess high antifungal and antibacterial activities.

Keywords: 1,2-Benzisothiazol-3(2*H*)-ones; Heterocyclic annelated isothiazol-3(2*H*)-ones; *S*-oxides; *S*-dioxides; Microbiocides; Toxicity

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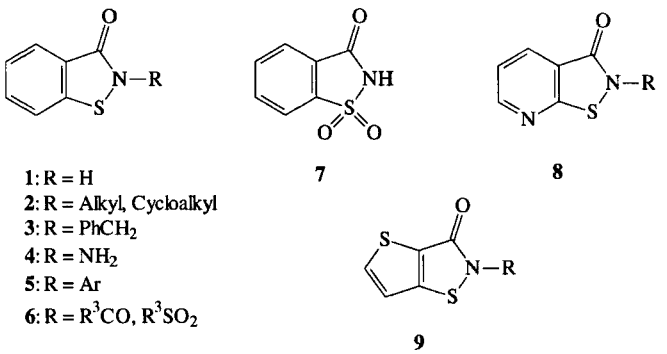
1. INTRODUCTION

It is known that 1,2-benzisothiazol-3(2*H*)-ones are a class of compounds with a wide spectrum of biological activities [1]. 1,2-Benzisothiazolone derivatives **1–6** have been reported to possess high antibacterial and antifungal activity [2]. A comprehensive review [3] of the biologically active 1,2-benzisothiazol-3(2*H*)-ones and derivatives has been published. The most best-known derivative is the noncaloric sweetening agent saccharin **7** [4,5], which was first synthesized by Remsen and Fahlberg (1879) by an oxidative cyclization of *ortho*-toluene-sulfonamide [6].

Although numerous 1,2-benzisothiazol-3(2*H*)-ones **1–6** are known [1,7–9] examples of isothiazol-3(2*H*)-ones fused to heterocyclic rings are relatively rare in the literature. Some isothiazolo[5,4-*b*]-pyridine-3(2*H*)-ones **8** have been reported in several patents [10a,b,11] and described to have fungicidal, bacteriocidal, and other similar biocidal activities [10a], to be inhibitors of blood platelet aggregation [10b] and antiacne agents [11]. Thieno[2,3-*d*]isothiazol-3(2*H*)-ones **9** were prepared by oxidation of 3,3′-dithiobis(2-thienocarboxamide) with SO_2Cl_2 (Scheme 1) [12].



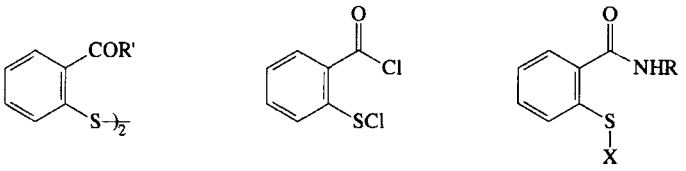
SCHEME 1

In this review we will describe the synthesis, reactions, and properties of heterocyclic annelated isothiazol-3(2*H*)-ones and 1,2-benzisothiazol-3(2*H*)-ones of the last decade.

2. PREPARATIONS

2.1. Synthesis of 1,2-Benzisothiazol-3(2*H*)-ones

1,2-Benzisothiazol-3(2*H*)-ones **1**–**6** are usually prepared by treatment of 2,2′-dithiobis-(benzoic acid) **10** with chlorine, bromine or sulfurylchloride via sulfenyl halogenide **13**, followed by an amine, acylamide or arylsulfonamide [1,7,9]. Several modifications of this method were used, including the reaction of 2,2′-dithiobis(benzamides) **12**, 2-mercaptobenzamides **14** or hydrazides **16** ($R = NHR^3$) with thionylchloride, via **15** for the syntheses of **2** (R = Alkyl), **3** ($R = PhCH_2$), **4** ($R = NH_2$), **5** (R = Aryl), and **6** ($R = R^3CO$), ($R = R^3SO_2$). This chemistry has been well reviewed (Schemes 1 and 2) [1,7,8].



10: R′ = OH
11: R′ = Cl
12: R′ = NHR

13

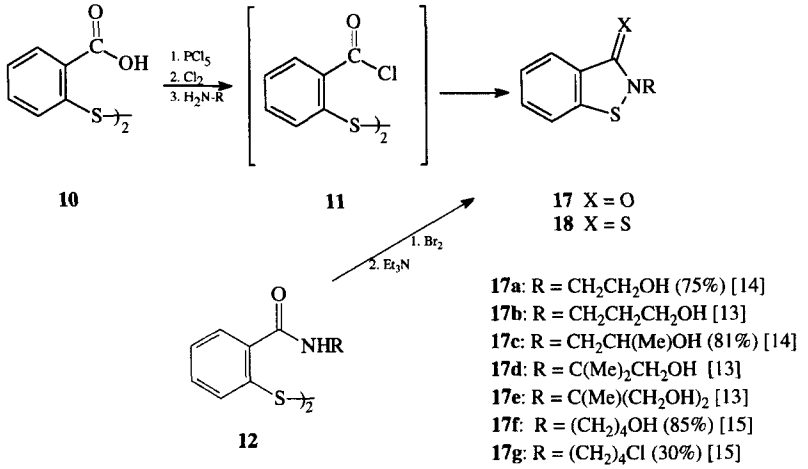
14: X = H
15: X = Cl
16: $R = NHR^3$

SCHEME 2

In this article, the following general syntheses of new substituted 1,2-benzisothiazol-3(2*H*)-ones employed in recent years are described: (i) cyclization of 2,2′-dithiobis-(benzoic acid) and derivatives via sulfenyl halogenides; (ii) intramolecular oxidative cyclization of 2-mercaptobenzamides, -benzoyl azides or -benzoates; (iii) ring closure of 2-alkylthio-, 2-*tert*-butylsulfinyl- or 2-benzylsulfinyl benzamides and benzaldehyde oximes; (iv) rearrangement of 3*H*-1,2-benzothiol-3-one 1-oxide; (v) ring contraction of 1,3-benzothiazines and thiepinones; and (vi) synthesis of 4,5,6,7-tetrahydro-1,2-benzisothiazol-3(2*H*)-ones.

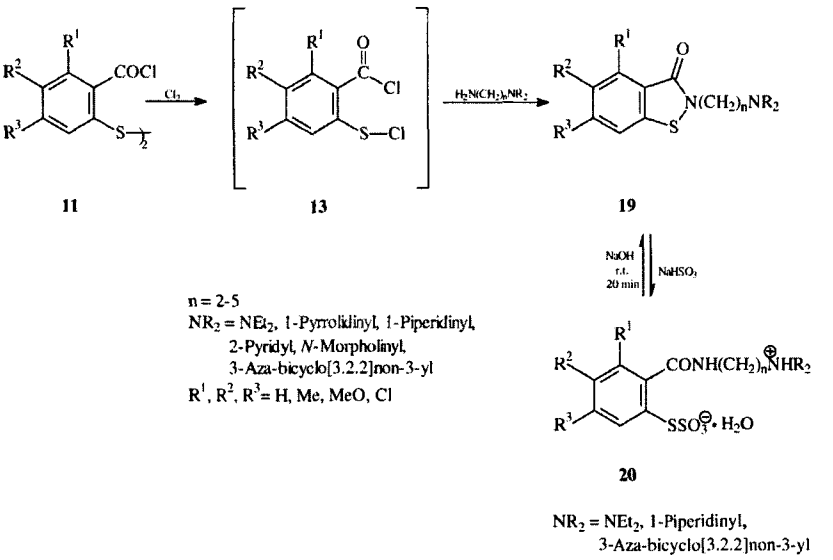
2.1.1. Cyclization of 2,2′-Dithiobis(benzoic acid) Derivatives via Sulfenyl Halogenides

Recently, new *N*-hydroxyalkyl derivatives of the 1,2-benzisothiazol-3(2*H*)-ones **17** and -thiones **18** (see Scheme 6) have been prepared and their antifungal and antibacterial activities were evaluated [13–16]; see Section 4. The derivatives **17** were synthesized from 2,2′-dithiobis(benzoic acid) **10** by treatment with phosphorus pentachloride according to the Mc Clelland procedure [16]. The intermediate **11** was not isolated but treated immediately with dry chlorine followed by the appropriate hydroxyalkylamine to give the desired **17a–g** (Scheme 3) [13]. The *N*-(2-hydroxyalkyl)-1,2-benzisothiazolones **17a, b** were prepared also from 2,2′-dithiobis(hydroxyalkylbenzamide) derivatives **12** through the cleavage of the S–S-bond by bromation and ring-closure with triethylamine (70–80%) [14].



SCHEME 3

N-Aminoalkyl-1,2-benzisothiazolones **19** (55 compounds) were synthesized in an analogous fashion from 2,2′-dithiobis(benzoic acid) and chlorines via the sulfenylchlorides **13** in 21–84% yield (Scheme 4) [17]. To prepare 5,6-dimethoxy-substituted compounds **19**, however, sulfurylchloride was used instead of chlorine to produce **13** ($R^2 = R^3 = MeO$).

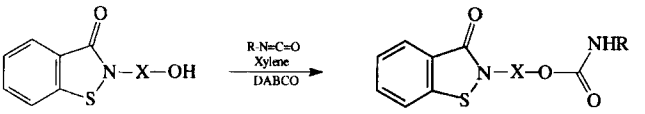


SCHEME 4

The *N*-aminoalkyl-1,2-benzisothiazolones **19** undergo ring opening when treated with a sodium hydrogen sulfite solution, giving Bunte salts **20** (59–83%) containing a substituted ammonium cation. Such salts are zwitterionic, as shown in structure **20**. The reconversion of **20** to benzisothiazol-3-ones **19** can be effected by diluted

alkali [18]. Several examples of the compounds **19** were potent inhibitors of adenosine diphosphate induced first-phase aggregation (see Section 4).

A series of *N*-(2-hydroxyalkyl)-1,2-benzisothiazol-3(2*H*)-one and thione carbamic esters **21–23** and **25** have been synthesized starting from **17a–c** or **18a** by treatment with the appropriate alkyl- and arylisocyanates in the presence of catalytic amounts of DABCO or $Fe(acac)_3$ (Scheme 5) [19–21].



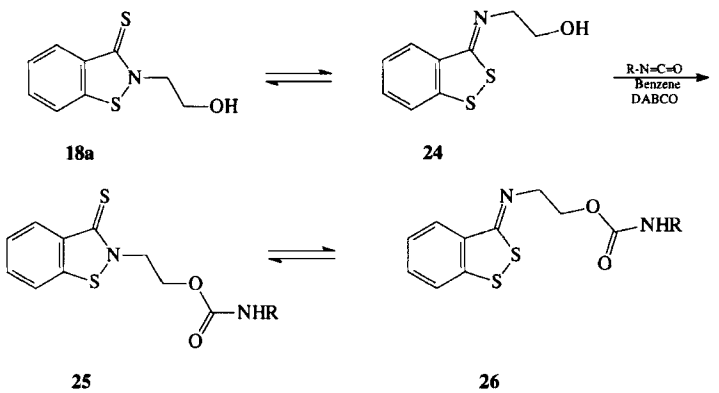
17a: X = $(CH_2)_2$ [14,20]
17b: X = $(CH_2)_3$ [13,20]
17c: X = CH_2-CH(Me) [14,20]

21: X = $(CH_2)_2$ (78-90%) [19-21]
22: X = $(CH_2)_3$ [20]
23: X = CH_2-CH(Me) [20]

R = Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, CH_2-CH=CH_2, C_6H_{11}, CH_2-CH_2-Cl, $PhCH_2$, Ph, 3-ClC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4 [19,20]

SCHEME 5

The 3-thiones **18a** and also **25** are in a dynamic equilibrium with the corresponding 3-imino-(3*H*)-1,2-benzodithiole derivatives **24** and **26** (Scheme 6) [19,22], see also Scheme 18. The antimicrobial properties are described in Section 4.



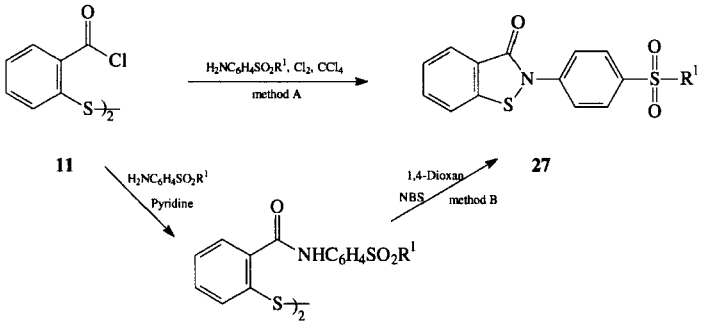
18a **24**

25 **26**

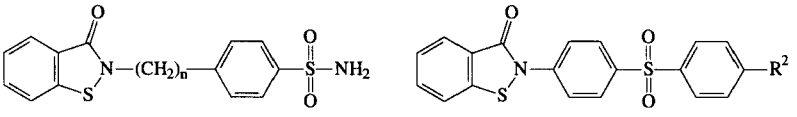
R = Et, *n*-Pr, *i*-Pr, *n*-Bu, *t*-Bu (65-75%) [19,21]

SCHEME 6

The synthesis of novel benzisothiazolone forms **27–29** were described by chlorination of disulfanes **11** via sulfenyl halogenide **13** and reaction with substituted sulfonyl aryl amides (Method A) [22]. The compounds **27** were also prepared from the corresponding disulfanes **12** in pyridine, by their reactions with *N*-bromosuccinimide in 1,4-dioxane (r.t., 3h, Method B) (Scheme 7 and Table I) [22]. BITAs **27–29** generally exhibited diminished antiviral potency when compared to their disulfane precursors **12** (see Section 4).



R^1 = NH_2, NHCOMe, NHCOPh, NH-2-pyrimidyl, NH-2-thiadiazolyl, NH-2-oxazolyl, NH-2-pyridyl, NH-2- thiazolyl, NH-3-isoxazolyl, NH-5-pyrazolyl, NH-3-pyridazinyl, guanidyl, NH-2-chinoxalinyl, NH-4-aminosulfonylphenyl

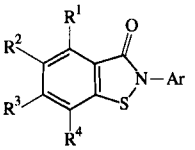


28a: n = 1
28b: n = 2

29
R^2 = NO_2, $NHSO_2C_6H_4NHCOCH_3$, $NHSO_2CH_2$-2-$NO_2C_6H_4$

SCHEME 7

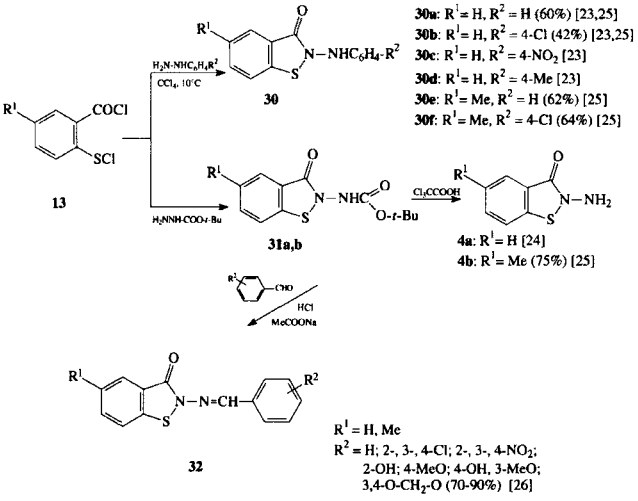
TABLE I 2-Aryl-1,2-benzisothiazol-3(2*H*)-ones **5a–o** and **27**



Cpd. No.	*Ar*	R^1	R^2	R^3	R^4	*Yield, %*	*Ref.*
5a	Ph	NO_2	H	NO_2	H	84	[33]
5b	4-BrC_6H_4	NO_2	H	NO_2	H	55	[33]
5c	4-$CF_3OC_6H_4$	NO_2	H	NO_2	H	76	[33]
5d	4-$CClF_2C_6H_4$	NO_2	H	NO_2	H	76	[33]
5e	Ph	H	H	H	H	75(A), 84(B), 72	[35a,36]
5f	Ph	H	NO_2	H	H	70(A)	[35a]
5g	3,4,5-$(MeO)_3$-C_6H_2	H	H	H	H	79(B), 76	[35a,36]
5h	3,5-$(MeO)_2C_6H_3$	H	H	H	H	62(B), 71	[35a,36]
5i	Ph	H	H	H	NO_2	75[a]	[35a]
5j	[b]	H	H	H	H	78	[35a]
5k	4-$MeOC_6H_4$	H	H	H	H	80, 68	[36,38]
5l	4-ClC_6H_4	H	H	H	H	64	[36]
5m	4-$COOEtC_6H_4$	H	H	H	H	35	[36]
5n	4-CNC_6H_4	H	H	H	H	32	[36]
5o	4-MeC_6H_4	H	H	H	H	64	[38]
27	$R^1NHSO_2C_6H_4$[c]	H	H	H	H	[d]	[22]
27a	$H_2NSO_2C_6H_4$	H	H	H	H	[d]	[22]
27b	$MeCONHSO_2C_6H_4$	H	H	H	H	87(B)	[22]

[a]Prepared directly from the sulfane; [b]Ar see Scheme 14; [c]R^1 see Scheme 7; [d]not given.

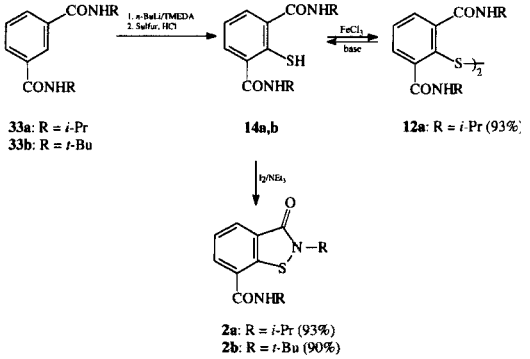
2-Amino derivatives **4a,b** have been prepared from *N*-(*tert*-butoxycarbonylamino)-1,2-benzisothiazol-3(2*H*)-ones **31a,b** derived from the suitable sulfenyl chloride **13** [24,25]. Condensation of **4a,b** with aldehydes afforded the hydrazones **32** in generally good yields (70–90%) [25,26]. Correlations between different hydrophobicity indices are reported and discussed (Scheme 8) [26]. The 2-anilino compounds **30** were prepared by direct reaction of the sulfenyl chloride **13** with the appropriate hydrazine derivatives [23,25].



SCHEME 8

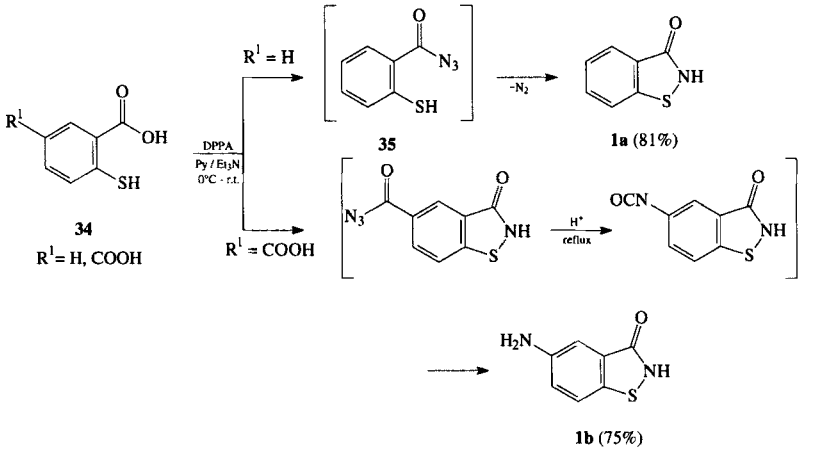
2.1.2. Intramolecular Oxidative Cyclization of 2-Mercaptobenzamides, -benzoyl azides or -benzoates

A further synthesis of benzisothiazole derivatives is described by *ortho*-lithiation of isophthalamides **33**. The reaction with elemental sulfur and HCl gives the thiol **14**. The addition of $FeCl_3$ produces the disulfane **12**, but only at a pH lower than 6. In the presence of a base the disulfane **12** will suffer disproportionation to give equimolar quantities of the starting material **14** and the benzisothiazole derivatives **2a,b**. Compounds **2a,b** could be obtained also by the direct oxidation of thiol **14** with iodine in the presence of NEt_3 (Scheme 9) [27].



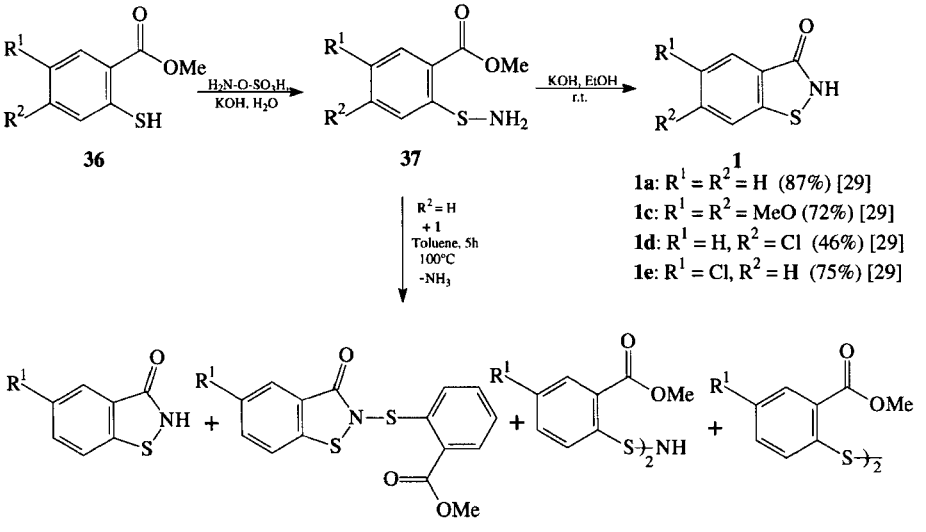
SCHEME 9

A convenient one pot synthesis of **1a** has been developed using a cyclization reaction in which the acyl azide **35** is used as an intermediate [28]. The structure of **1a** was determined by X-ray crystallography analysis. At high temperature (100°C), **34a** ($R^1 = H$) cyclized to 2-hydroxy-1,3-benzothiazole via Curtius rearrangement (67%). Finally, the synthesis of the 5-amino derivative **1b** was reported (Scheme 10) [28].



SCHEME 10

The synthesis of 1,2-benzisothiazol-3(2*H*)-ones **1a** and **1c–e** by cyclization under basic conditions of the isolated 2-methoxycarbonyl benzenesulfenamides **37**, which were prepared from amination of thiosalicylates **36** by hydroxylamine-*O*-sulfonic acid, was examined and is a new facile chlorine-free synthesis of **1** (Scheme 11) [29].

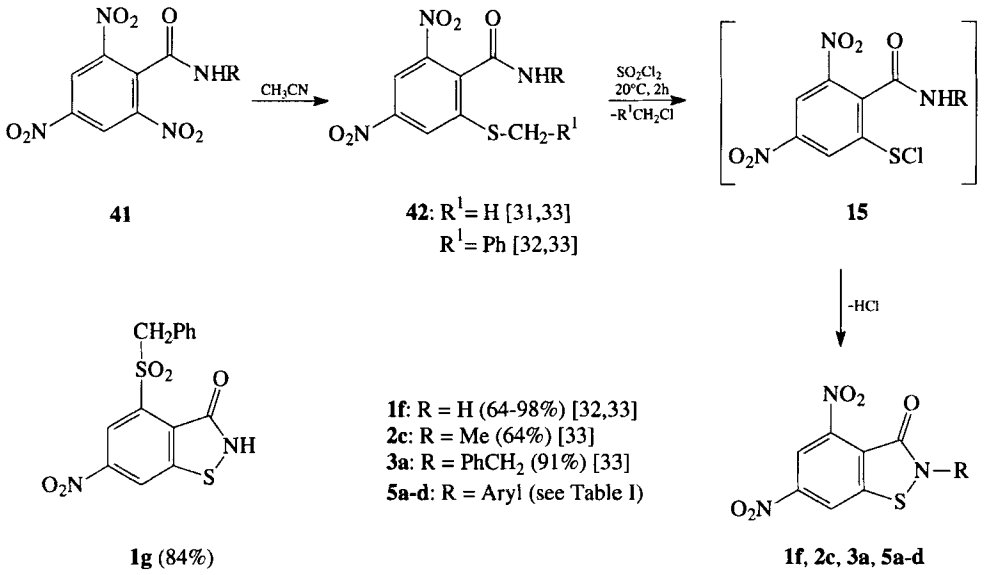


SCHEME 11

Unexpectedly, the 2-sulfenyl derivatives **38** were obtained as major products when the cyclization of **37** was carried out at 100°C in the absence of base [29,30]. In this reaction, **1** attacked the sulfur atom of the sulfenamide **37**, and ammonia was eliminated, as a result, the 2(2-methoxycarbonylphenylthio)-1,2-benzisothiazolone **38** was formed. In the same manner the benzenesulfenamide **39** was formed when ammonia was eliminated from two molecules of **37** [30]. Derivatives **39** and **40** were obtained as by-products.

2.1.3. Ring Closure of 2-Alkylthio-, 2-tert-Butylsulfinyl- or 2-Benzylsulfinyl-benzamides and Benzaldehyde Oximes

1,2-Benzisothiazolones are also prepared by chlorination of 2-alkylthio benzamides [31–33], e.g. **42**. Thus, regioselective nucleophilic substitution of the nitro group in 2,4,6-trinitrobenzamides **41** leads to *ortho*-benzylthiobenzamides **42** (R^1 = Ph) which gives sulfenyl chlorides **15** upon treatment with SO_2Cl_2 at room temperature. The products **15** spontaneously cyclize to form 4,6-dinitro-1,2-benzisothiazol-3-ones **1f**, **2c**, **3a**, **5a–d** (Scheme 12). 2-Benzylthio-4-nitrobenzamide containing other electron withdrawing groups at the 4-position react similarly, e.g. to **1g** (84%) [31,32].



41

42: R^1 = H [31,33]
R^1 = Ph [32,33]

15

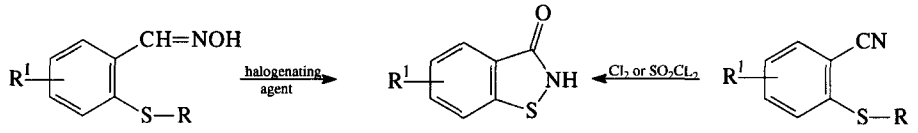
1f: R = H (64-98%) [32,33]
2c: R = Me (64%) [33]
3a: R = $PhCH_2$ (91%) [33]
5a-d: R = Aryl (see Table I)

1g (84%)

1f, 2c, 3a, 5a-d

SCHEME 12

A method for preparation of 1,2-benzisothiazolones **1** by the reaction of either the benzaldehyde oximes **43** or the 2-alkylthio-benzonitrile **44** with a halogenating agent has been described (Scheme 13) [34].

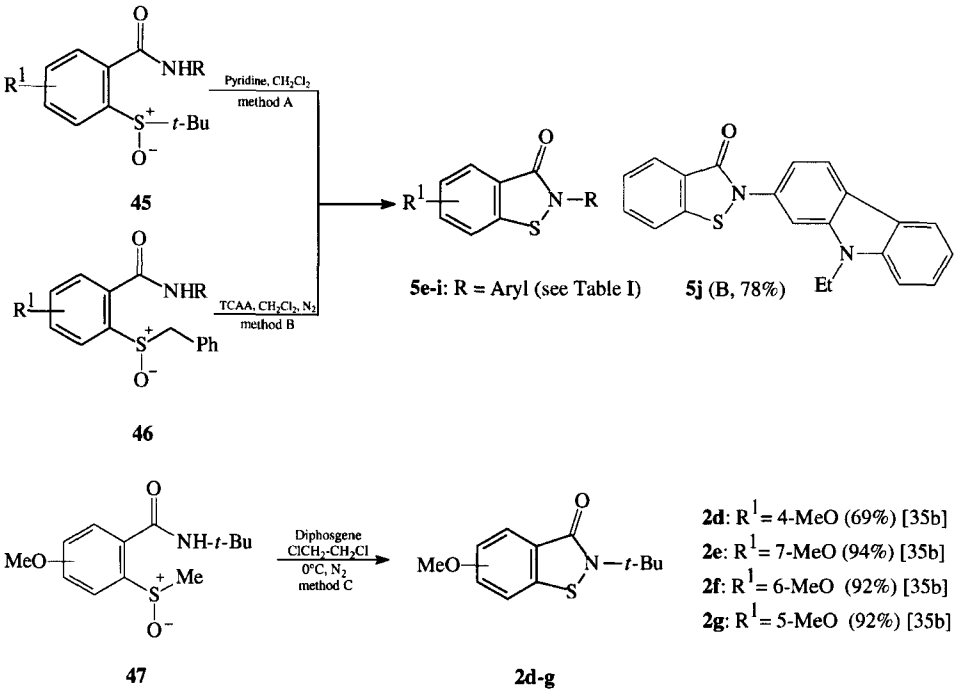


43 **1** **44**

R = Alkyl
R^1 = H, Alkyl (C_{1-4}), Alkoxy, NO, COOH, Cl

SCHEME 13

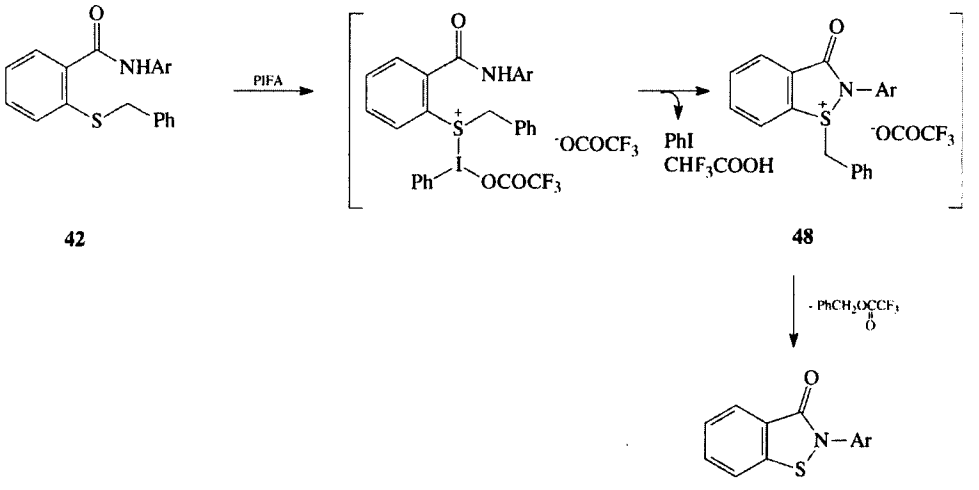
A new synthetic route is described for the synthesis of benzisothiazolones **5e–j** from *tert*-butylsulfinyl **45** (Method A) or benzylsulfinyl substituted carboxamides **46** (Method B) that provides a mild alternative to conventional cyclization methods that employ halogens (Scheme 14) [35a]. The cyclization of sulfoxide **47** to **2d–g** with diphosgene was achieved in the usual manner (Method C) [35b,c]. The purification of 2-substituted **2** (R = Alkyl) are realized by addition of acids to **2**, isolation of the resulting salts, and dissociation of the salts [35d].



SCHEME 14

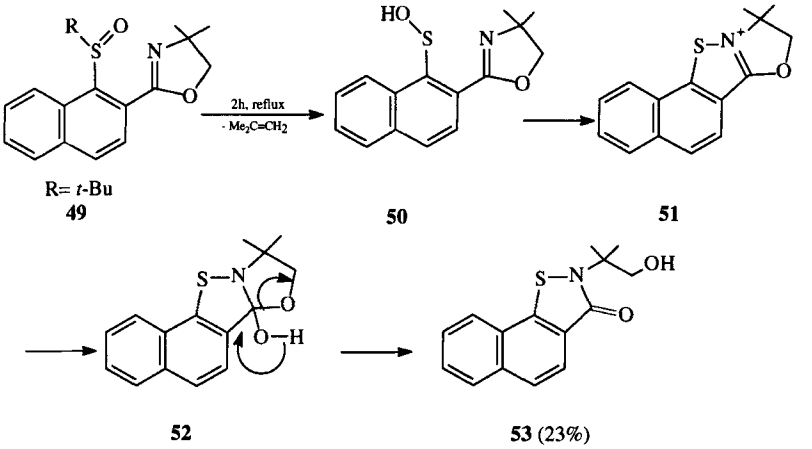
Treatment of *N*-aryl-2(benzylthio)benzamides **42** with phenyliodine(III)-bis(trifluoroacetate) containing trifluoroacetic acid resulted in an interrupted Pummerer-type reaction to give the compounds **5** rather than the normal Pummerer-type

products (Scheme 15). Moreover, the *N*-(4-nitrophenyl) substrate **42** ($R^3 = 4\text{-}NO_2$) proved unreactive [36].



SCHEME 15

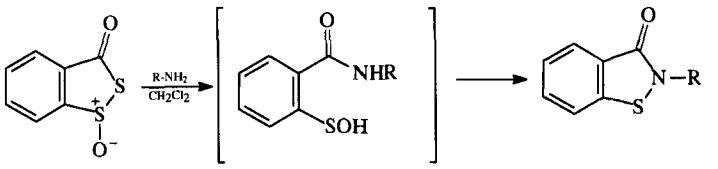
It is known that sulfoxides having at least one alkyl substituent with a hydrogen atom attached to the β-carbon atom can undergo thermal decomposition to alkenes and sulfenic acids, which normally undergo intermolecular disproportionation. The sulfoxide **49**, on account of the large number of available β-hydrogen and in order to relieve strain, undergoes thermal elimination of isobutene. The resulting sulfenic acid **50** is trapped by an intramolecular electrophilic addition reaction followed by addition of water to the iminium double bond, ring-opening and a prototropic shift that yields the isothiazolones **53** (Scheme 16) [37].



SCHEME 16

2.1.4. Rearrangement of 3H-1,2-Benzodithiol-3-one 1-Oxide

Reaction of 3*H*-1,2-benzodithiol-3-one 1-oxide **54** with primary amines or anilines provides a new access to the corresponding 1,2-benzisothiazol-3(2*H*)-ones **1**, **2**, and **5** by ring-arrangement in reasonable yields. This reaction offers a new method for the preparation of special 1,2-benzisothiazol-3(2*H*)-ones (Scheme 17) [38]. Two compounds **2i** and **5k** prepared by this method have been characterized by X-ray crystallography.

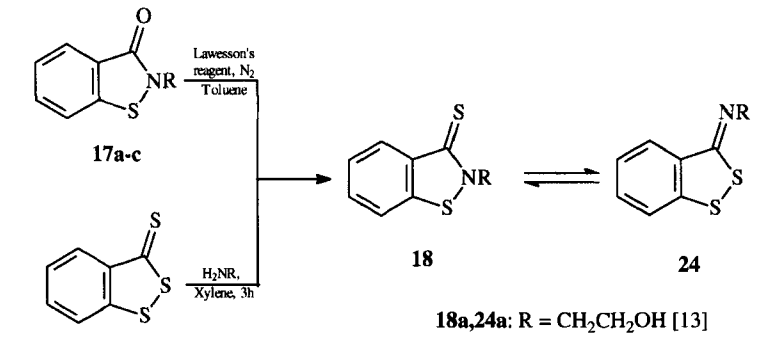


54 **55**

1a: R = H (55%)
2h: R = Cyclohexyl (39%
2i: R = CH_2CH_2Ph (60%)
5k,o: see Table I

SCHEME 17

Thus, *N*-substituted thiones **18** were synthesized by treatment of 3*H*-1,2-benzodithiol-3-thione **56** with hydroxyalkylamines to give mixtures of thiones **18** and 3-imino-1,2-benzodithioles **24**. Better yields of **18** were obtained by sulfuration of the corresponding 1,2-benzisothiazolone derivatives **17a–c** with Lawesson's reagent (Scheme 18) [13].



17a-c **18** **24**

56

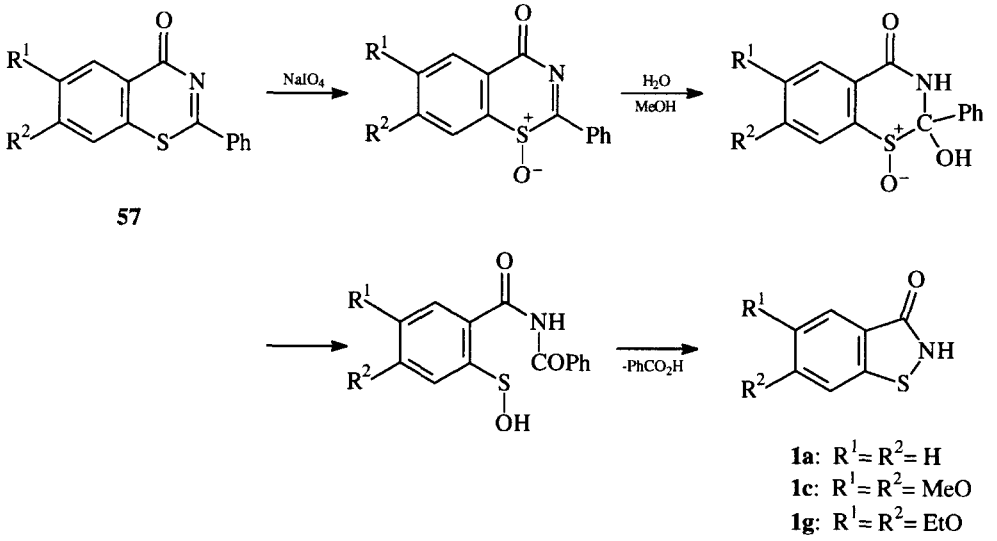
18a,24a: R = CH_2CH_2OH [13]
18b,24b: R = $CH_2CH_2CH_2OH$ [13]
18c,24c: R = $CH_2CH(Me)OH$ [13]
18d,24d: R = CMe_2CH_2OH [13]
18e,24e: R = $CMe(CH_2OH)_2$ [13]

SCHEME 18

2.1.5. Ring Contraction of 1,3-Benzothiazines and Thiepinones

A new synthesis of *N*-unsubstituted 1,2-benzisothiazolones **1** by an oxidative ring contraction of 1,3-benzothiazines has been described. Treatment of the 4-oxo-1,3-benzothiazine derivatives **57** with sodium periodate in aqueous methanol resulted in ring

contraction to give the 1-oxides of **1a,c,g** (58–90%), see **140a** and **140b**$_{1,2}$ (Section 3.3). The reaction proceeds by addition of water followed by ring-opening and then loss of benzoic acid (Scheme 19) [39]. The 1-oxide of **1a** was also prepared through oxidation of 2,2′-dithiobis(benzamide) with sodium periodate (72%). When the sulfoxide of **57c** was stirred in aqueous methanol until complete dissolution, the isothiazolone **1c** was isolated from the reaction mixture in high yield (86%).

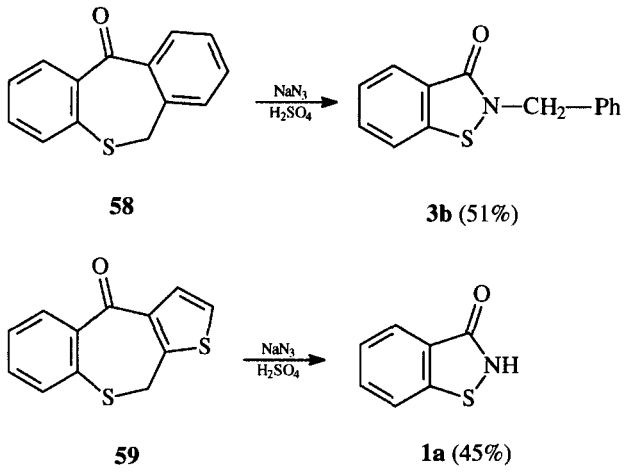


57

1a: $R^1 = R^2 = H$
1c: $R^1 = R^2 = MeO$
1g: $R^1 = R^2 = EtO$

SCHEME 19

The Schmidt reaction with NaN_3 of the thiepinones **58** and **59** resulted in ring contraction and formation of the 1,2-benzisothiazolones **1a** and **3b** (Scheme 20) [12], see Section 2.2.4.



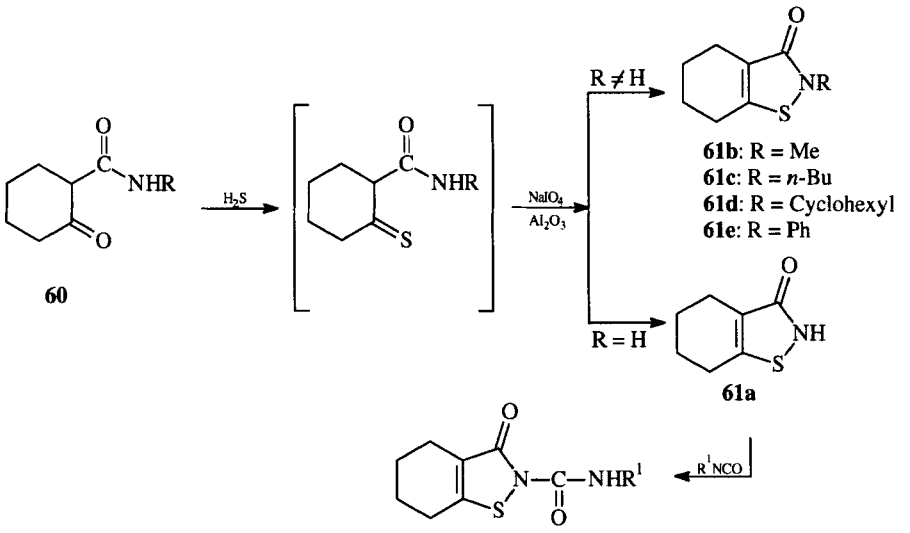
58 **3b** (51%)

59 **1a** (45%)

SCHEME 20

2.1.6. Synthesis of 4,5,6,7-Tetrahydro-1,2-benzisothiazol-3(2H)-ones

4,5,6,7-Tetrahydro-1,2-benzisothiazolones **61** are prepared by cyclization of 2-oxocyclohexane-1-carboxamides **60** with H_2S (Scheme 21) [40a–c].

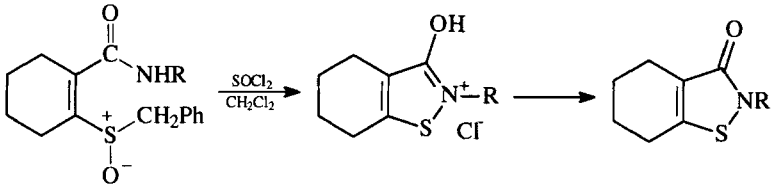


60

61f: R^1 = Me
61g: R^1 = *i*-Pr
61h: R^1 = Cyclohexyl
61i: R^1 = Ph

SCHEME 21

The reaction of 2-benzylsulfinyl cyclohexene-1-carboxamides **62** in dichloromethane and thionylchloride yields tetrahydrobenzisothiazolone derivatives **61** which are antibacterial agents (Scheme 22) [41a–c].

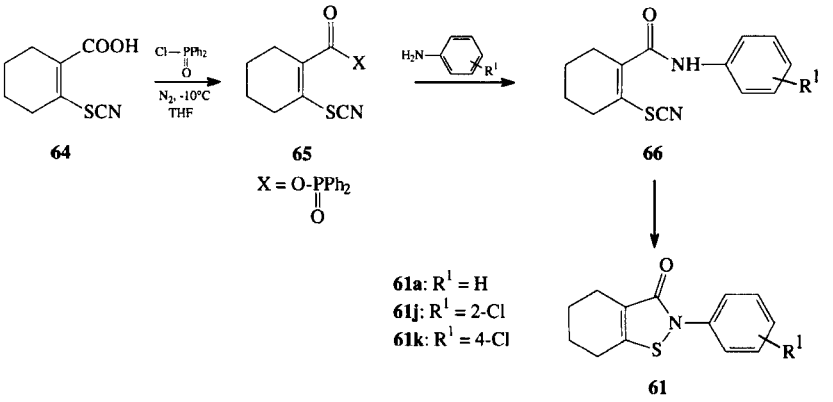


62 **63**

61a: R = H
61e: R = Ph

SCHEME 22

A new synthetic approach to *N*-aryl substituted derivatives **61** was found by cyclocondensation of 2-thiocyanocyclohexene-1-carboxamides **66**, which were prepared from the carboxylic acid **64** via the thiocyanate **65** (Scheme 23) [42].

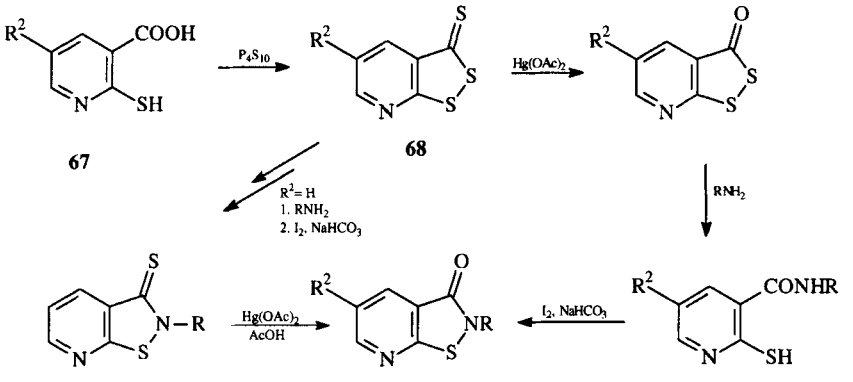


SCHEME 23

2.2. Synthesis of Heterocyclic Annelated Isothiazol-3(2*H*)-ones

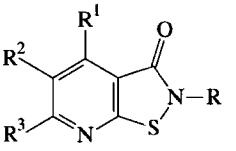
2.2.1. Isothiazolopyridine-3(2H)-ones

Isothiazol-3(2*H*)-ones annelated to heterocyclic rings are relatively rare in the literature. The first method described the synthesis of 2-substituted isothiazolo[5,4-*b*]pyridine-3(2*H*)-ones **8** [10a,b]. The starting material chosen was the readily accessible 2-mercapto-3-pyridinecarboxylic acid **67**, which on treatment with P_4S_{10} gave the 3*H*-1,2-dithiolo[3,4-*b*]pyridine-3-thione **68**. Reaction of this compound with mercuric acetate yielded the 3-oxo analogue, which gave the carboxamides **70** when heated with amines. Cyclization of **70** to isothiazolo[5,4-*b*]pyridine-3(2*H*)-ones **8h–i** and **71a,b** was achieved by oxidation with iodine in the presence of sodium bicarbonate (Table II) (Scheme 24) [10b,43a,c] (see also **8b–g** in [43b]). Compound **68** reacts with primary alkyl amines to give 2-mercapto-3-pyridinecarbothioamides (75–83%) and two minor products, **69** (R = *n*-Alkyl, $PhCH_2$) and 3-imino-3*H*-1,2-dithiole[3,4-*b*]pyridine [43b]. The isothiazol-3(2*H*)-thiones **69b–g** gave after desulfurization with $Hg(OAc)_2$ the 3-oxo derivatives **8b–g** (35–40%) [43d].



SCHEME 24

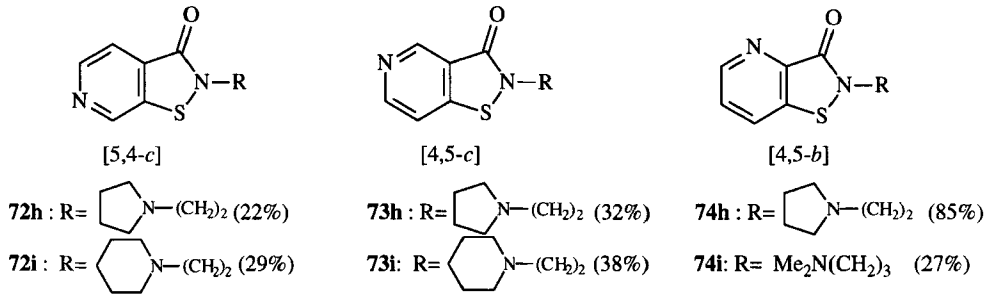
TABLE II 2,3-Dihydroisothiazolo[5,4-*b*]pyridine-3(2*H*)-ones **8a–i**, **71a,b** (R = Alkyl), **78a–f** (R = H) and **94a–e** (R = CH_2CO_2Et)



Cpd. No.	*R*	R^1	R^2	R^3	*Yield, %*	*Ref.*
8a	Me	H	H	H	30	[44]
8b	*n*-Pr	H	H	H	[a]	[43b,d]
8c	*n*-Bu	H	H	H	4	[43b,d]
8d	*n*-Amyl	H	H	H	[a]	[43b,d]
8e	n-C_6H_{13}	H	H	H	36	[43b,c,d]
8f	$Ph(CH_2)_2$	H	H	H	[a]	[43b,d]
8g	$Ph(CH_2)_3$	H	H	H	[a]	[43b,d]
8h	pyrrolidin-2-yl-$(CH_2)_2$	H	H	H	67	[43a]
8i	pyridin-2-yl-$(CH_2)_2$	H	H	H	61	[43a]
71a	$Et_2N(CH_2)_2$	H	Ph	H	61	[43a]
71b	4-Me-thiazol-2-yl-$(CH_2)_2$	H	Ph	H	29	[43a]
78a	H	H	H	H	27(66)	[44,52]
78b	H	Me	H	Me	65(68)	[46,50a,69]
78c	H	Ph	H	Ph	84(60)	[50a,50b]
78d	H	Me	H	Ph	53	[50a]
78e	H	Ph	H	Me	73	[50a]
78f	H	H	$CONH_2$	NH_2	74	[51]
94a	CH_2CO_2Et	H	NH_2	H	84(B)	[53]
94b	CH_2CO_2Et	H	Me	H	41(A), 61(B)	[53]
94c	CH_2CO_2Et	H	Ph	H	40(A), 60(B)	[53]
94d	CH_2CO_2Et	H	H	H	75(A), 80(B)	[53]
94e	CH_2CO_2Et	H	NO_2	H	80(A), 77(B)	[53]

[a]By-products in small quantity.

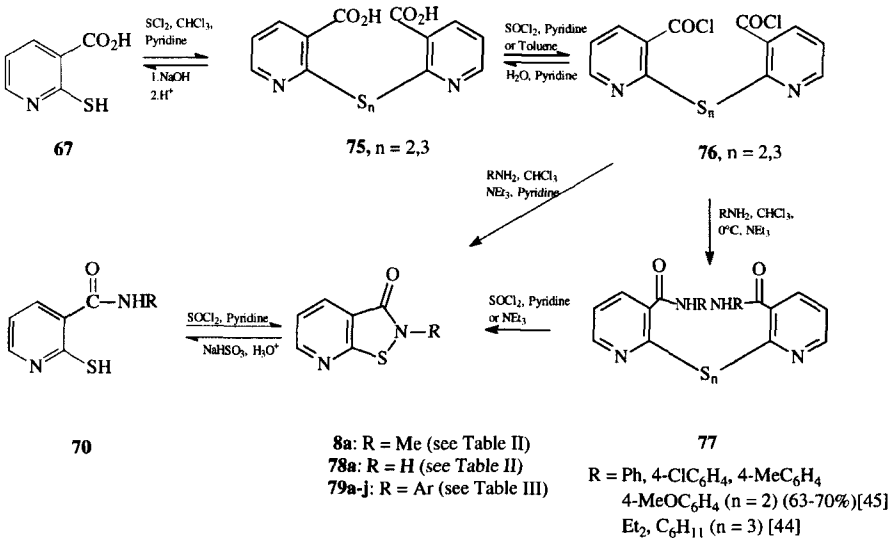
This synthesis is also applicable to all isomeric isothiazolopyridin-3(2*H*)-ones **72–74** (Scheme 25) [43a].



SCHEME 25

The 2-mercapto-3-pyridinecarboxylic acid **67** reacts with SCl_2 to give the 2,2′-trithiobis-(3-pyridinecarboxylic acid) **75**($n = 3$) which on treatment with thionyl chloride gave **76** ($n = 3$). On the other hand, **67** reacted with $SOCl_2$ to give the 2,2′-dithiobis-3-pyridinecarbonyl chloride **76**($n = 2$). The latter hydrolyzed to the corresponding dithio

acid **75** [44]. **76** also reacted with amines in chloroform at 0°C to give 2,2′-dithiobis-3-pyridinecarboxamides **77**, which on treatment with triethylamine in CH_2Cl_2 gave the 2-mercapto-3-pyridinecarboxamides **70** and the isothiazolones **8a** and **79d,e** [44]. The reaction of **76** ($n = 2$) with ammonium hydroxide gave **70** (R = H) (27%) and **78a** (R = H, 27%). In the same manner the reaction of **76** ($n = 2$) with amines in chloroform gave at room temperature the isothiazolo[5,4-*b*]-pyridine-3(2*H*)-ones **8a** and **79b–e** [44]. The 2-aryl and 2-heteroaryl compounds **79a,d,f–j** were also obtained by treatment of 3-pyridinecarboxamides **70** with thionyl chloride–pyridine in good yields (70–92%) or from the reaction of bisamides **77** with $SOCl_2$ and NEt_3 or pyridine, see Table III (Scheme 26) [45].

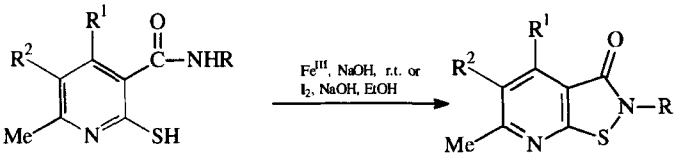


67 **75**, n = 2,3 **76**, n = 2,3

70 **8a**: R = Me (see Table II) **78a**: R = H (see Table II) **79a-j**: R = Ar (see Table III) **77** R = Ph, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$ 4-MeOC$_6$H$_4$ (n = 2) (63-70%)[45] Et$_2$, C$_6$H$_{11}$ (n = 3) [44]

SCHEME 26

Isothiazolo[5,4-*b*]pyridine-3(2*H*)-ones **81a–n** (R^3 = Me) are obtained when 2-mercapto-3-pyridinecarboxamides **70** are oxidized with iodine or potassium hexacyanoferrate-(III) (Table IV) (Scheme 27) [46].

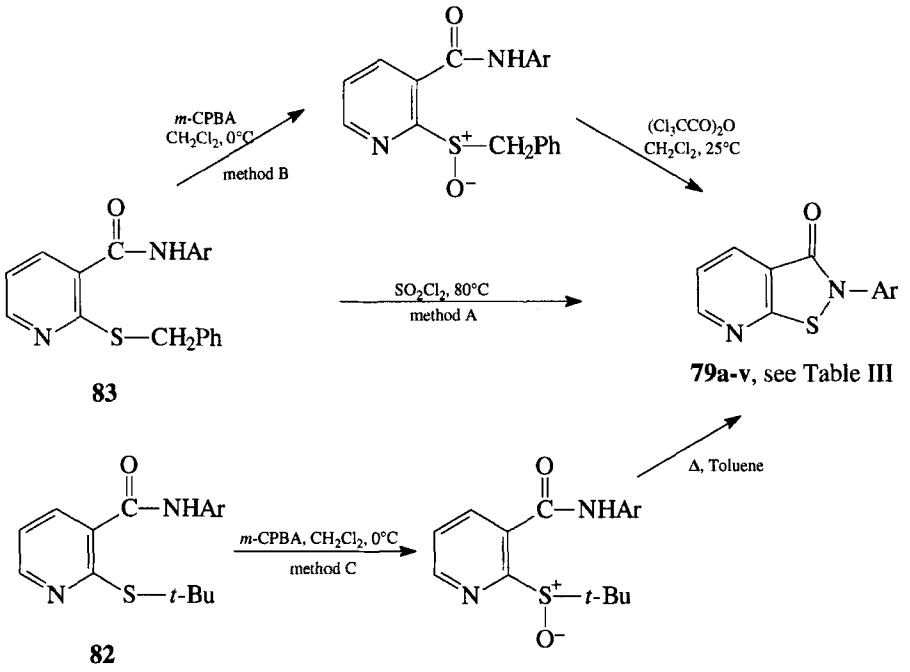


70 **81a-n**: (see Table IV)

SCHEME 27

The 2-arylisothiazol-3-ones **79** were also prepared from 2-benzyl- or 2-*tert*-butylthio-3-pyridinecarboxamides **82** and **83** by oxidative cyclization. Benzylsulfanes **83** were simultaneously dealkylated and cyclized to the isothiazolones **79** either by oxidation with sulfuryl chloride at 80°C (Method A) or by oxidation to

the 2-benzylsulfinyl-3-pyridinecarboxamides with *meta*-CPBA at 0°C followed by treatment with trichloroacetic anhydride at 0°C (Method B) [47] in analogy to the 1,2-benzisothiazolones [35] (see Section 2.1.3). *Tert*-butyl sulfides were oxidatively dealkylated, and cyclized to **79** by oxidation to the sulfoxide with *meta*-CPBA at 0°C followed by thermolysis in refluxing toluene (Method C) [47] (Scheme 28). Oxidative deprotection of 5-benzylthioether **83** (R = Ph) with sulfuryl chloride afforded the sulfenyl chlorides, which were treated *in situ* with DABCO to furnish **79a** [48].

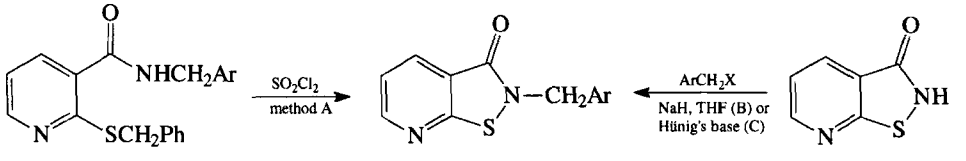


83 **79a-v**, see Table III

82

SCHEME 28

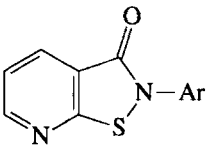
A series of 2-benzylisothiazol-3(2*H*)-ones **84** were prepared also by oxidative cyclization of **83** (R = $ArCH_2$) with sulfuryl chloride (Method A) or alkylation of **78a** by the benzyl bromide under basic conditions. This was accomplished by the use of either NaH in THF (Method B) or Hünig's base in EtOH (Method C), see Table V [49]. 2-Pyridine-, 2-furanyl and 2-thienylmethyl derivatives were synthesized [49] (see Section 3).



83 **84a-r**, see Table V **78a**

SCHEME 29

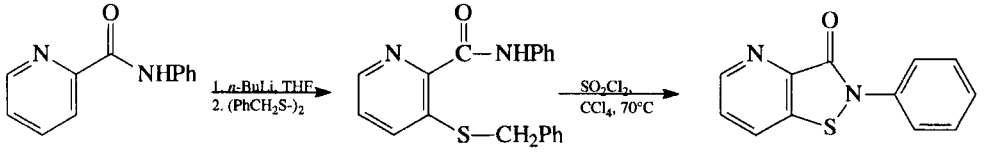
TABLE III 2-Aryl- and Heteroaryl-2,3-dihydroisothiazolo[5,4-*b*]pyridine-3(2*H*)-ones **79a–v**



Cpd. No.	*Ar*	*Method*[a]	*Yield, %*	*Ref.*
79a	Ph	A,B,C[b]	87[c](91,75)[b] 80	[35a,45,48,47]
79b	2,6-$Me_2C_6H_3$	A	35(88)	[44,47]
79c	4-$NO_2C_6H_4$[f]	A	43(91)	44,47]
79d	4-$MeOC_6H_4$[f]	B[b],A	30(88[c],81[b],51)	[35a,44,45,47]
79e	Cyclohexyl		82[d]	[44]
79f	4-ClC_6H_4[f]	A	90[c],97	[45,47]
79g	4-MeC_6H_4[f]		92[e]	[45]
79h	2-pyr[g]	A	70[e](5)	[45,47]
79i	2-pyrm[h]		77[e]	[45]
79j	2-thz[i]		75[e]	[45]
79k	4-FC_6H_4	A	89	[47]
79l	4-BrC_6H_4	B	72	[47]
79m	4-IC_6H_4	B	77	[47]
79n	4-$CF_3C_6H_4$	A	34	[47]
79o	2,4-$(MeO)_2C_6H_3$[f]	C	94	[47]
79p	2,4,6-$(MeO)_3C_6H_2$[f]	B	84	[47]
79q	3-OHC_6H_4	B	35	[47]
79r	2,6-(*iso*-Pr)$_2C_6H_3$	B	60	[47]
79s	4-$AcNHC_6H_4$[f]	C	50	[47]
79t	4-$MeSO_2NHC_6H_4$	C	59	[47]
79u	4-$CO_2MeC_6H_4$[f]	B	53	[47]
79v	4-CNC_6H_4	B	60	[47]

[a]Method by which benzyl sulfide (A), benzyl sulfoxide (B), and *tert*-butyl sulfoxide (C) was oxidatively cyclized to isothiazolones [47]; [b][35a]; [c]prepared directly from the disulfane **77** ($n = 2$) [45]; [d]prepared from the trisulfane **77** ($n = 3$) [44]; [e]prepared from the carboxamide **70** [45]; [f]substituents at 2-aryl ring in 2-, 3- or/and 4-position: NO_2, MeO, Cl, AcNH, CO_2Me [47]; [g]2-Pyridyl-; [h]2-Pyrimidyl-; [i]2-Thiazolyl-.

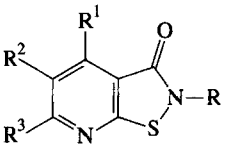
The isothiazolo[4,5-*b*]pyridine-3(2*H*)-one **74a** was prepared by the reaction of an organolithium species with **85** and the dibenzyl disulfane to give **86** which was simultaneously dealkylated and cyclized to **74a** by oxidation with sulfuryl chloride at 70°C (Scheme 30) [47].

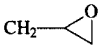
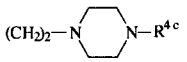
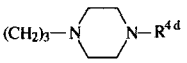
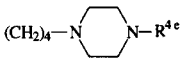
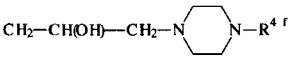
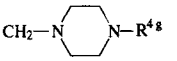


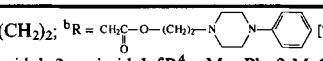
85 **86** **74a** (77%)

SCHEME 30

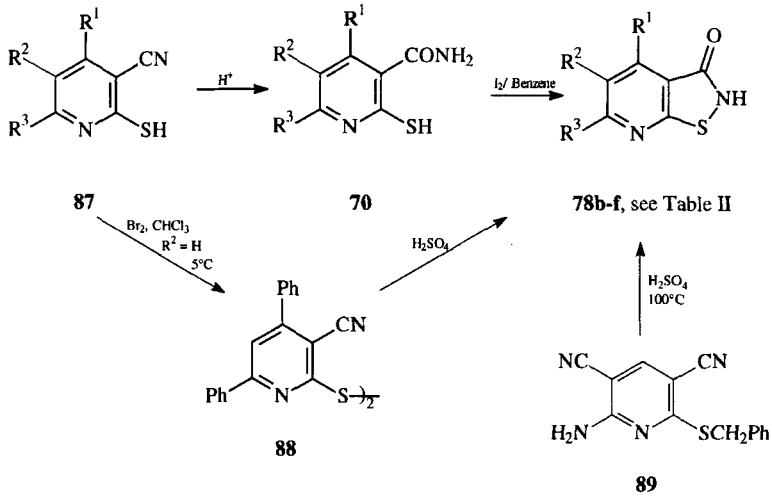
TABLE IV 2,3-Dihydroisothiazolo[5,4-*b*]pyridine-3(2*H*)-ones **81a–s**, **125a–d**, **127a–d**, and **129**



Cpd. No.	*R*	R^1	R^2	R^3	*Yield, %*	*Ref.*
81a	n-C_8H_{17}	Me	H	Me	88	[46]
81b	Cyclohexyl	Me	H	Me	94	[46]
81c	$PhCH_2$	Me	H	Me	95	[46]
81d	[a]	Me	H	Me	89	[46]
81e	2-pyridyl-$(CH_2)_2$	Me	H	Me	82	[46]
81f	4-ClC_6H_4	Me	H	Me	78	[46]
81g	2,4-$Cl_2C_6H_3$	Me	H	Me	90	[46]
81h	2,6-$Cl_2C_6H_3$	Me	H	Me	74	[46]
81i	$PhCH_2O$	Me	H	Me	–	[46]
81j	$PhCH_2$	CF_3	H	Me	–	[46]
81k	4-ClC_6H_4	CH_3	H	Me	53	[46]
81l	4-$MeOC_6H_4$	H	H	Me	75	[46]
81m	2,6-$Cl_2C_6H_3$	H	H	Me	71	[46]
81n	2,6-$Cl_2C_6H_3$	H	Me	H	78	[46]
81o		Me	H	Me	38	[68]
81p	CH_2COOH	Me	H	Me	–	[51b]
81p$_1$	[b]	Me	H	Me	–	[51b]
81q	CH_2COOEt	H	$CONH_2$	NH_2	61	[51a]
81r	$CH_2CH{=}CH_2$	H	$CONH_2$	NH_2	70	[51a]
81s	$PhCH_2$	H	$CONH_2$	NH_2	70	[51a]
125a	CH_2CH_2OH	Me	H	Me		[67]
125b	CH_2CH_2Cl	Me	H	Me	60	[67]
125c	CH_2CH_2Br	Me	H	Me		[67]
125d	$(CH_2)_4Br$	Me	H	Me		[67]
127a$_{1-4}$		Me	H	Me	55–71	[67]
127b$_{1-6}$		Me	H	Me	47–52	[67,70]
127c$_{1-3}$		Me	H	Me	70–74	[67,70]
127d$_{1-8}$		Me	H	Me	60–83	[68,70]
129		Me	H	Me	55–85	[68,70]

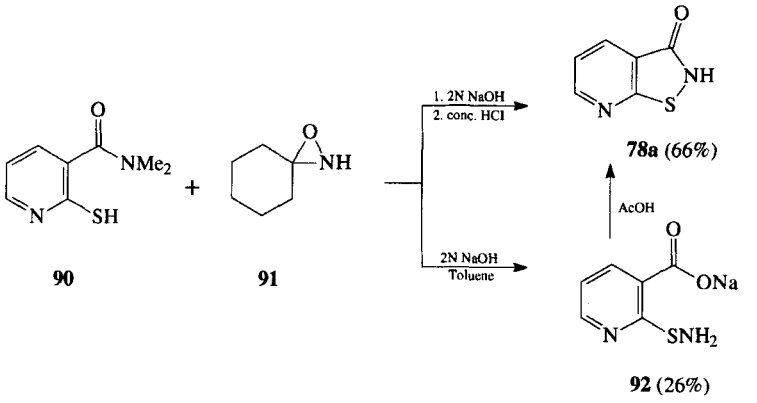
[a] *N*-morpholino-$(CH_2)_2$; [b] R =  [70]; [c] R^4 = Me, Ph, 2-pyridyl, 2-pyrimidyl; [d] R^4 = Me, Ph, 3-ClC_6H_4, 3-$CF_3C_6H_4$, 2-pyridyl, 2-pyrimidyl; [e] R^4 = Me, Ph, 2-$MeOC_6H_4$; [f] R^4 = Me, Ph, 2-, 3- and 4-ClC_6H_4, 3-$CF_3C_6H_4$, 2-pyridyl, 2-pyrimidyl; [g] R^4 = Me, 2-, 3- and 4-ClC_6H_4, 2-$MeOC_6H_4$, 2-pyridyl, 2-pyrimidyl, *trans*-cinnamyl.

The acidic hydrolysis of 3-cyano-2-mercaptopyridines **87** gives the 2-mercapto-3-pyridinecarboxamides **70** (R^1, R^3 = Me or Ph, $R^2 = H$), which was treated with H_2SO_4 [50a] or iodine in benzene [50b], see also [10a]. At refluxing temperature the carboxamide **70** gives the isothiazolo[5,4-*b*]-pyridine-3(2*H*)-ones **78b–e** in 55–60% yield, see Table II (Scheme 31) [50a]. It is also possible to obtain **78c** via the disulfane **88** [50a]. The 5-carboxamido-6-amine derivative **78f** was obtained by acid hydrolysis of 2-amino-3,5-dicyanopyridine, arylmethyl-substituted at position 6 [51]. The *N*-alkylation of **78f** is described in Section 3.1.



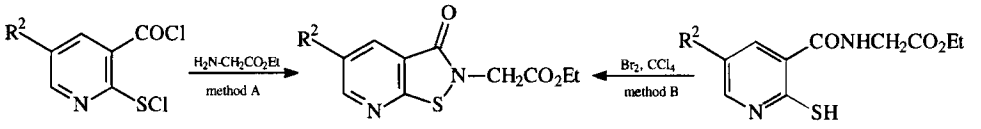
SCHEME 31

Reaction of 2-mercaptonicotinic acid dimethylamide **90** and oxaziridine **91** gave in the two-phase system toluene–2N NaOH the crystalline amination–hydrolysis product **92**. On acidification it cyclizes to isothiazolo[5,4-*b*]pyridine-3(2*H*)-ones **78a**, which can be obtained also without isolation of intermediate **92** by working up with hydrochloric acid (Scheme 32) [52].



SCHEME 32

A new series of 5-substituted ethyl 3-oxoisothiazolo[5,4-*b*]pyridine-2-acetates **94a–e** were prepared either directly by reaction of 5-substituted 2-chlorosulfenyl-3-pyridinecarbonyl chlorides **93** with ethyl glycinate (Method A) or by oxidation of the corresponding 2-mercapto-3-pyridinecarboxamides **70** (Method B) for their further study as antiinflammatory agents (Scheme 33) [53].

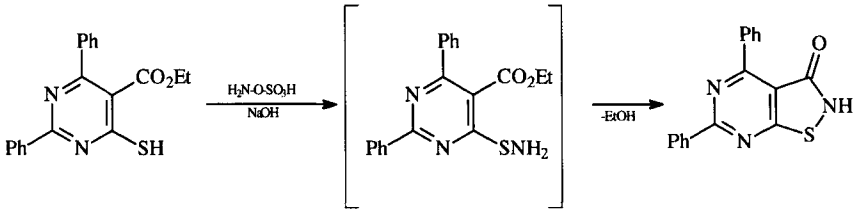


93 **94a-e**, see Table II **70**

SCHEME 33

2.2.2. *Isothiazolopyrimidine-3(2H)-ones*

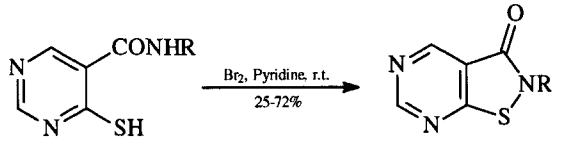
The first isothiazolo[5,4-*d*]pyrimidine **96a** was obtained by treatment of **95** with hydroxylamine-*O*-sulfonic acid (Scheme 34) [54].



95 **96a** (53%)

SCHEME 34

The oxidative cyclization of carboxamides **97** with Br_2 in pyridine results in the formation of isothiazolo[5,4-*d*]pyrimidines **96b–j** (Scheme 35) [46].

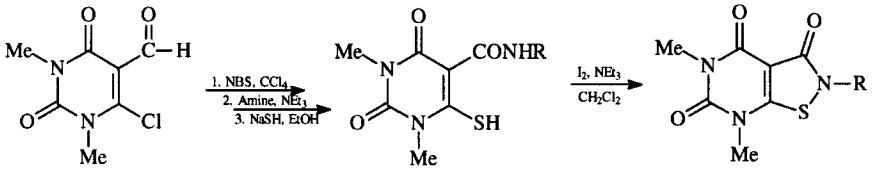


97 **96**

96b: R = H (69%)
96c: R = Me (41%)
96d: R = *n*-C_8H_{17} (53%)
96e: R = Cyclohexyl (64%)
96f: R = $PhCH_2$ (48%)
96g: R = Pyridin-2-yl-$(CH_2)_2$ (30%)
96h: R = 4-ClC_6H_4 (38%)
96i: R = 2,6-$Cl_2C_6H_3$ (25%)
96j: R = 3-$CF_3C_6H_4$ (72%)

SCHEME 35

A new general synthetic route for the preparation of **100** started with *N*,*N*-dimethylbarbituric acid, Vilsmeier reaction to **98**, followed by conversion of the aldehyde to the acid bromide by heating with NBS in CCl_4, cooling to $-78°C$ and slow addition of the amine and external base triethylamine. Displacement of the Cl with NaSH in ethanol to **99** was accomplished at r.t. with short reaction times. Oxidation to the corresponding **100** was carried out using I_2 and triethylamine in CH_2Cl_2 (Scheme 36) [55].

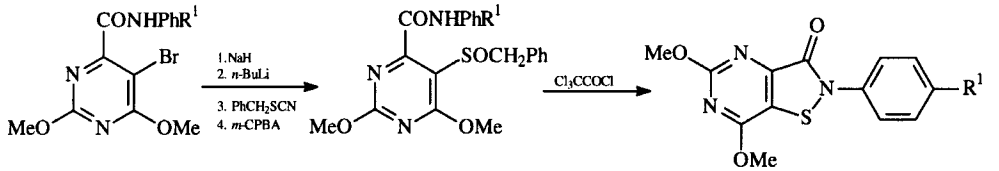


98 **99**

100a: R = H
100b: R = 4-BrC_6H_4
100c: R = $PhCH_2$

SCHEME 36

The *N*-unsubstituted constitutional isomers **103**, were prepared via a similar route, starting with orotic acid via **101** to **102** (Scheme 37) [47,55]. The use of the more electrophilic benzylthiocyanate gave 5-benzylsulfanes as desired, which were readily oxidized with *meta*-CPBA to their corresponding sulfoxides **102**. Ring closure to get the isothiazolones **103a–c** was accomplished with trichloroacetyl chloride in methylene chloride.



101 **102**

103a: R^1 = H (48%) [47,55]
103b: R^1 = MeO (50%) [47,55]
103c: R^1 = CF_3 (67%) [47,55]

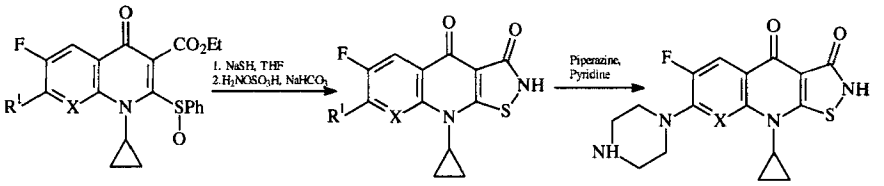
SCHEME 37

In summary, it is shown that 2-substituted isothiazolopyridine-3(2*H*)-ones **8**, **71–74,78,79**, and **81** and pyrimidines **97**, **100**, and **103** are usually constructed by oxidation of 2-mercapto-3-pyridinecarboxamides **70** or 4-thioxo-5-pyrimidinecarboxamides **97** with *meta*-periodate [11], iodine [43a,46,50a,55], potassium hexacyanoferrate-(III) [46], thionyl chloride [45] or bromine in pyridine [46]. Similary 2,2′-dithiobis- or 2,2′-trithiobis-3-pyridinecarboxamides **77** were oxidized to 2-arylisothiazolo[5,4-*b*]pyridinones **79** [44,45]. An alternative route to **79** and **84** has been described by oxidative cyclization of 2-benzylthio- or *tert*-butylthio-3-pyridinecarboxamides **82** and **83** with sulfuryl chloride at 80°C or by oxidation to the sulfoxide with *meta*-CPBA

at 0°C followed by treatment with trichloroacetic anhydride [35,47–49], see also **102–103** [47,55].

2.2.3. 2,3,4,9-Tetrahydro-isothiazolo[5,4-b]chinoline- and Isothiazolo-[5,4-b]-[1,8]naphthylridine-3,4-dione

9-Cyclopropyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]chinoline **106a,c** (Scheme 38) [56a] and isothiazolo[5,4-*b*]-[1,8]-naphthylridine-3,4-dione **106b** were prepared by cyclization of the 3-carboxylic acid ester **104** [57]. Regiospecific displacement of the sulfinyl group of the sulfoxide **104** was accomplished with sodium hydrogensulfide in aqueous tetrahydrofuran yielding a 2-mercapto intermediate. This intermediate reacts without purification with hydroxylamine-*O*-sulfonic acid to give a hydrosulfamine derivative which cyclized *in situ* to yield **105**.



104

105a: R^1 = Cl; X = N (71%) [57]
105b: R^1 = Cl; X = CF (67%) [57]
105c: R^1 = F; X = CH (85%) [56a,b]

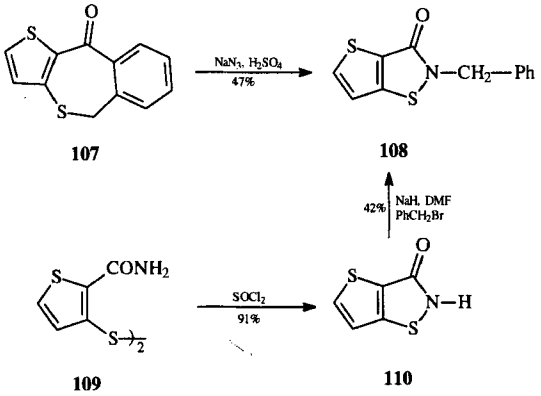
106a: X = CH (85%) [56a]
106b: X = N (94%) [57]
106c: X = CF (74%) [57]

SCHEME 38

The compounds **106b,c** display high antibacterial activity [57–59].

2.2.4. Thienoisothiazolo-3(2H)-ones

N-Benzylthieno[2,3-*d*]isothiazole-3(2*H*)-one **108** can be prepared by the Schmidt reaction with NaN_3 from thiepinone **107** or by oxidation of 3,3′-dithiobis(2-thienocarboxamide) **109** via **110** (Scheme 39) [12].

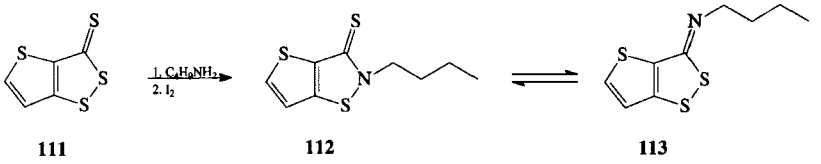


107 **108**

109 **110**

SCHEME 39

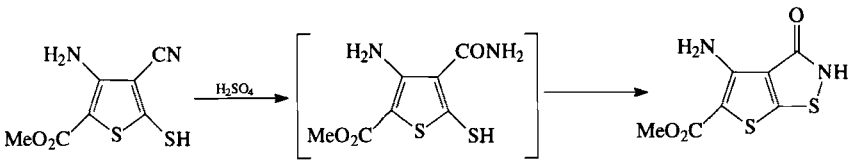
The reaction of 3*H*-thieno[3,2-*c*]-1,2-dithiol-3-thione **111** with 1.2 equivalents of *n*-butylamine afford the *N*-butylthieno[3,2-*c*]isothiazol-3(2*H*)-thione **112** which is in a dynamic equilibrium with its 3*H*-thieno[3,2-*c*]-1,2-dithiole-*N*-butyl-3-imino isomer **113** (Scheme 40) [60].



111 **112** **113**

SCHEME 40

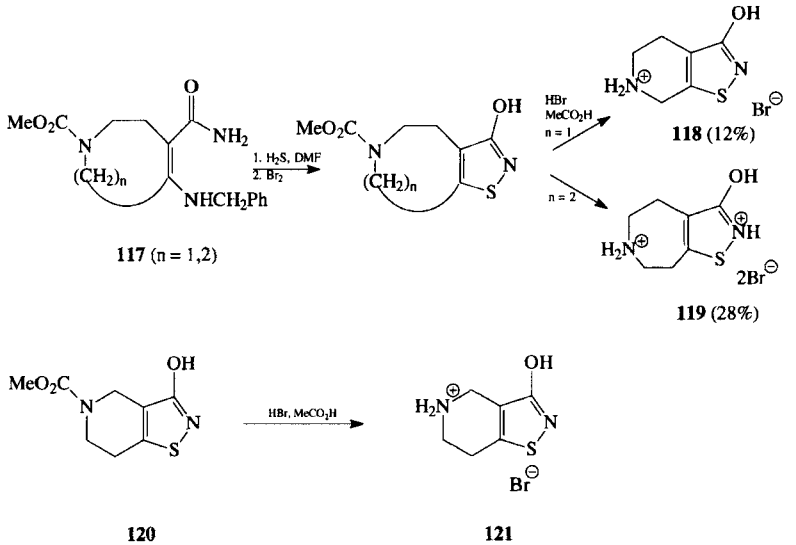
Thieno[3,2-*d*]isothiazolone **116** was synthesized by ring closure treating mercaptan **114** with H_2SO_4 (Scheme 41) [61].



114 **115** **116**

SCHEME 41

The reaction of **117** with H_2S and bromine gave the isothiazolone hydrobromides **118** and **119** (Scheme 42) [62]. The salt **121** was obtained in a similar manner [62,63].



120 **121**

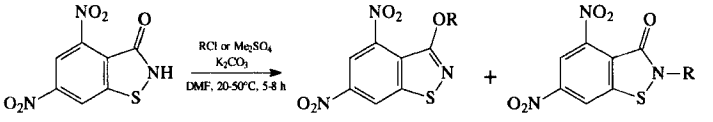
SCHEME 42

3. REACTIONS

3.1. *O*/*N*-Functionalization

A series of alkylation [7] and acylation reactions [1,7] of unsubstituted 1,2-benzisothiazolones **1** have been investigated previously. Here the *O*- and *N*-functionalizations of donor and acceptor substituted 1,2-benzisothiazolones **1a,e,f** and pyridoisothiazolones **78a,b,f** are described.

Thus, **1f** reacts with dimethylsulfate and benzyl chloride in DMF in the presence of K_2CO_3 to afford mixtures of 3-alkoxy-4,6-dinitro-1,2-benzisothiazoles **2c'**, **2f'**, **3a'**, and 2-alkyl derivatives **2c**, **3a** in which the products of *O*-alkylation are the principal components [33]. Both products of *O*- and *N*-alkylation can easily be separated due to their different solubility in hexane. Reaction of **1f** with ethyl chloroacetate under the same conditions affords only the *O*-alkylation product **2f'** (Scheme 43).



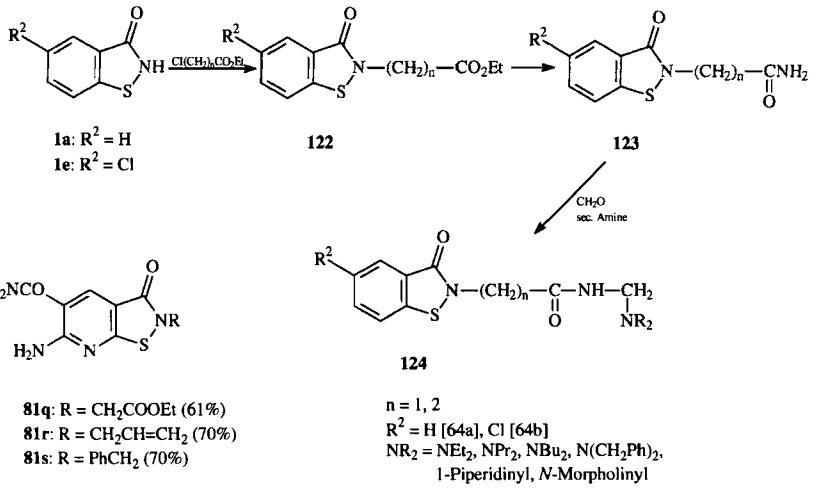
1f

2c': R = Me (60%)
2f': R = CH_2CO_2Et (44%)
3a': R = $PhCH_2$ (44%)

2c: R = Me (22%)
3a: R = $PhCH_2$ (15%)

SCHEME 43

In the search for novel pharmacologically active compounds the 1,2-benzisothiazolone-amides **123**, 3-oxo-1,2-benzisothiazol-2-acetates and 2-propionates **122** were also obtained by alkylation of **1a,e**. In the reaction of these amides **123** with formaldehyde and various secondary amines the aminomethyl derivatives **124** are formed (Scheme 44) [64,65]. The pyridoisothiazolone **78f** ($R^2 = CONH_2$, $R^3 = NH_2$) reacts by alkylation to give **81q–s** [51a].



1a: R^2 = H
1e: R^2 = Cl

122

123

124

81q: R = CH_2COOEt (61%)
81r: R = $CH_2CH{=}CH_2$ (70%)
81s: R = $PhCH_2$ (70%)

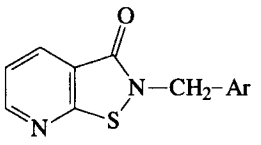
n = 1, 2
R^2 = H [64a], Cl [64b]
NR_2 = NEt_2, NPr_2, NBu_2, $N(CH_2Ph)_2$, 1-Piperidinyl, *N*-Morpholinyl

SCHEME 44

2-Arylmethylisothiazolo[5,4-*b*]pyridine-3(2*H*)-ones **84a–r** were obtained also by alkylation of **78a** with benzyl bromides under basic conditions, see Table V and Scheme 29 [49].

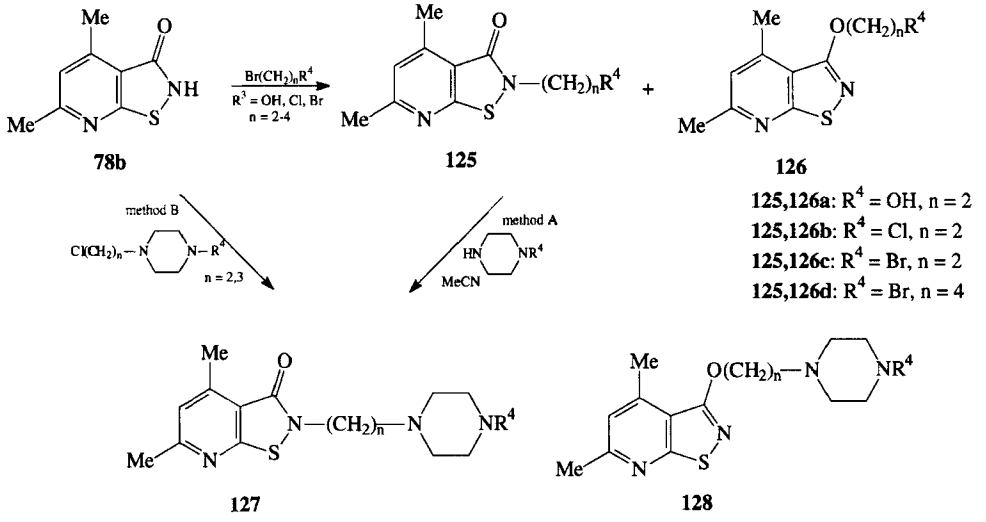
N-(Piperazin-1-ylalkyl)-3-oxoisothiazolopyridines **127** and **129** are biologically active compounds and show anorectic and antimycobacterial activities. These compounds were synthesized by alkylation of the *N*-unsubstituted isothiazolopyridine **78b** (Schemes 45 and 46) [66–72]. The K-salt of the 4,6-dimethyl derivative **78b** [66] was alkylated with alkyl bromides to yield mixtures of *N*- and *O*-alkylated products **125** and **126**, from which **125** and **126** were isolated by chromatography [67,71]. The reaction of the compound **125** (R^3 = Cl or Br, n = 2–4) with *N*-substituted piperazines in aprotic solvents (MeCN, xylene) gave **127a$_{1-4}$**, **127b$_2$**, and **127c$_{1,2}$** in 55–74% yields (Method A). Alternatively, when mixtures of **125** and **126** were used in a similar reaction and the products separated by chromatography, **127** (n = 3,4) and **128** (n = 3, R^4 = Ph) were obtained. The synthesis of the compounds with a 2–3 carbon chain (Method B) involved the condensation of equimolar amounts of **78b** and the appropriate 1-chloroalkyl substituted piperazine in the presence of NaOEt. The piperazine derivatives **127c** were synthesized in 20–55% yields by the reaction of the K-salt of **78b** with 1-haloalkyl-4-substituted piperazines.

TABLE V 2-(Arylmethyl)-2,3-dihydroisothiazolo[5,4-*b*]pyridine-3(2*H*)-ones **84a–r**



Cpd. No.	*Ar*	*Method*[a]	*Yield, %*	*Ref.*
84a	Ph	A(B)	86	[35,43d,48,49]
84b	4-$NO_2C_6H_4$	C	25	[49]
84c	4-$CO_2MeC_6H_4$[b]	B	15	[49]
84d	4-CNC_6H_4[b]	B	27	[49]
84e	4-ClC_6H_4[b]	C	21	[43a,49]
84f	4-$CF_3C_6H_4$	C	62	[49]
84g	4-$MeOC_6H_4$[b]	C	41	[49]
84h	2,5-$(MeO)_2C_6H_3$	C	20	[49]
84i	4-$C_6H_5C_6H_4$	C	13	[49]
84j	4-pyr[c]	A	61	[49]
84k	3-pyr[c]	A	91	[49]
84l	2-pyr[c,e]	A	77	[49]
84m	2-pyrm[c]	C	–	[49]
84n	2-fur[d,f]	C	31	[49]
84o	3-fur[d]	C	27	[49]
84p	2-thie[d,f]	B	30	[49]
84q	3-thie[d]	B	21	[49]
84r	4-thz[d]	B	17	[49]

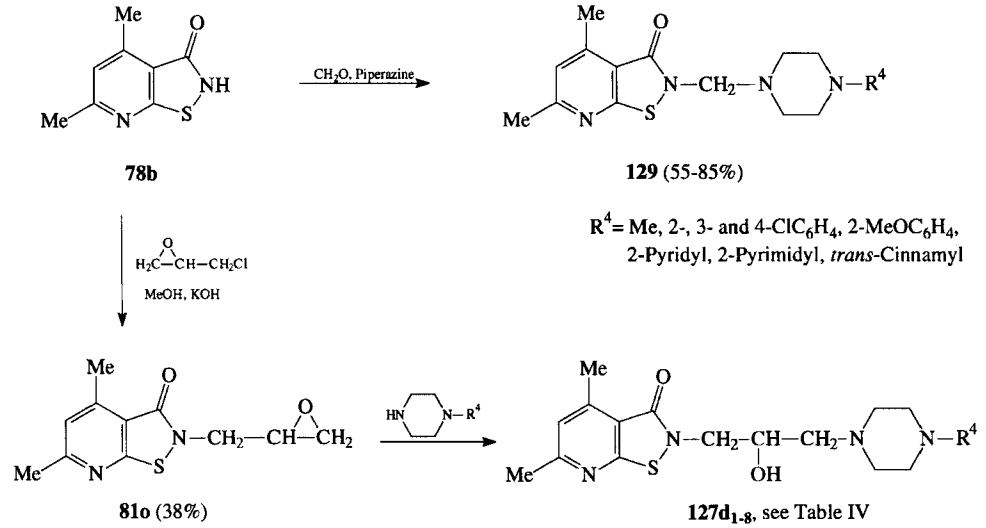
[a]Method A: oxidative cyclization of **83** by heating with sulfuryl chloride: *N*-alkylation, Method B: NaH in THF, Method C: Hünig's base in EtOH; [b]substituents at 2-aryl ring in 2- or 3-position: CO_2Me, CN, Cl, MeO; [c]2-, 3- or 4-Pyridyl, 2-pyrimidyl; [d]2- or 3-Furyl, 2- or 3-thienyl, 4-thiazolyl; [e]substituents at 2-pyridyl ring in 3-, 5- or 6-position: CO_2Me; [f]substituents at 2-furyl- and 2-thienyl ring in 3-, 4- or 5-position: CO_2Me, CO_2Et, CN, COOH.



127a$_{1-4}$: R^4 = Me, Ph, 2-Pyridyl, 2-Pyrimidyl; n = 2
127b$_{1-6}$: R^4 = Me, Ph, 3-ClC_6H_4, 3-$CF_3C_6H_4$, 2-Pyridyl, 2-Pyrimidyl; n = 3
127c$_{1-3}$: R^4 = Me, Ph, 2-$MeOC_6H_4$; n = 4

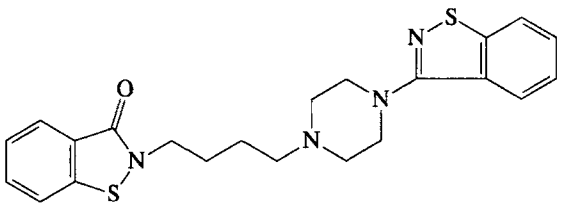
SCHEME 45

2-Piperazinylmethyl substituted isothiazolo[5,4-*b*]pyridine-3(2*H*)-ones **129** were prepared by the Mannich reaction of **78b** with CH_2O and appropriately 4-R^4-substituted piperazines for screening as CNS active agents (Scheme 46) [68,70]. The compounds **127d$_{1-8}$**, containing a 2-hydroxypropyl chain were prepared from the ring-opening reactions of **81o** with *N*-substituted piperazines in 60–83% yield.



SCHEME 46

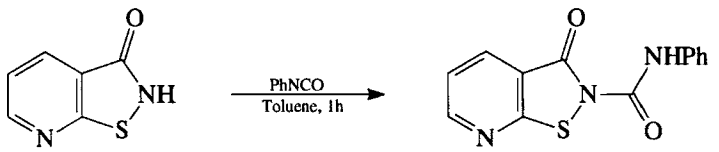
A novel piperazinyl derivative **2o** was prepared and evaluated as a potential antipsychotic agent (Scheme 47) [15].



2o

SCHEME 47

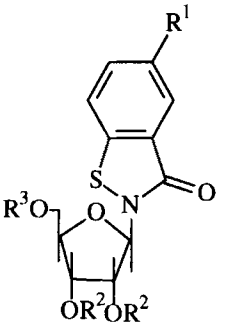
The reaction of 2-hydroxyalkyl-1, 2-benzisothiazolones **17a–c** with alkylisocyanates results in the formation of carbamic esters **21–23** (see Scheme 5). On the other hand, the reaction of **78a** with phenylisocyanate gives the 2-carbamoyl derivate **130** (Scheme 48) [52].



78a **130** (89%)

SCHEME 48

The study of the biocidal activity of the 1,2-benzisothiazol-3(2*H*)-ones was extended to the synthesis of β-ribonucleosides containing a 1,2-benzisothiazole ring. The reaction of the silylated base of 5-methyl-1,2-benzisothiazol-3(2*H*)-one **1g** (R^1 = 5-Me) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose followed by basic deprotection gave the corresponding crystalline ribonucleosides **131** (Scheme 49) [73].



131

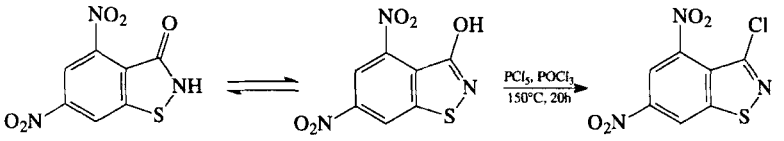
131a: R^1 = Me, R^2 = R^3 = PhCO (69%)

131b: R^1 = Me, R^2 = R^3 = H (89%)

131c: R^1 = Me, R^2 = Me_2C<, R^3 = H (36%)

SCHEME 49

It was found that the carbonyl group in **1f** can be replaced with chlorine, probably via the tautomer **1f'**. Thus **1f** reacts with a mixture of PCl_5 and $POCl_3$ to give the 3-chloro derivative **132** in 65% yield (Scheme 50) [33,74].

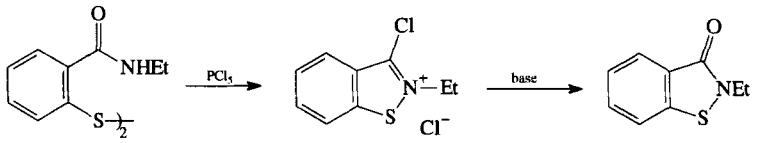


1f **1f'** **132**

SCHEME 50

The preparation of 3-chloro-2-butyl-pyridoisothiazolium chloride as an intermediate which reacts with ammonium hydrate to give **8c** and the 3-imino derivative, has been reported [43b].

The disulfane **12** reacts with PCl_5 to give the 3-chloro salt **133**. This salt is a versatile compound, e.g. heating it with diethylamine gives 3-diethylamino-1,2-benzisothiazole and treatment with base yields 1,2-benzisothiazolone **2p** (Scheme 51) [1].



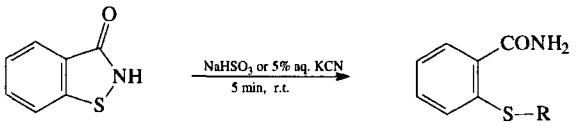
12 **133** **2p**

SCHEME 51

3.2. Ring Opening Reactions

An electrophilic attack at the nitrogen atom or a nucleophilic attack at the sulfur atom of the ambiphilic reaction center of the S–N bond are possible. The nucleophilic cleavage of the S–N bond of isothiazolones is reversible.

Thus, the S–N bond in **1a** was attacked by SO_3^{2-} leading to the Bunte salt **134a** in 55% yield. Similarly, the product of the reaction of **1a** with cyanide ion (5% aqueous KCN, 5 min at r.t.) was the thiocyanate **134b** (Scheme 52) [18].

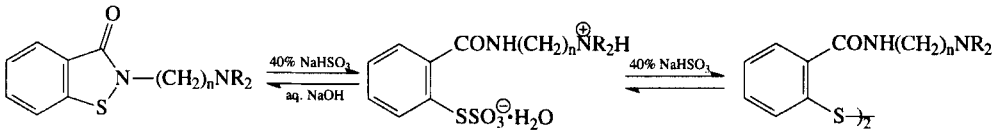


1a

134a: R = $SO_3Na \cdot H_2O$
134b: R = CN

SCHEME 52

Treatment of 2-substituted 1,2-benzisothiazolones **19** (see Scheme 4) with 40% aqueous $NaHSO_3$ also gave Bunte salts **20**, but these was not simply *N*-substituted analogues of **134a**. Elemental analysis, however, showed that sodium was absent. Such salts **20** are zwitterionic [18]. The salts **20** are reconverted into the corresponding **19** with dilute alkali (e.g. **19d**, 65%). In addition, **20** were also formed from disulfanes **135** with $NaHSO_3$. It is therefore possible to obtain 1,2-benzisothiazolone **19** from **135** via Bunte salts **20** (Scheme 53).



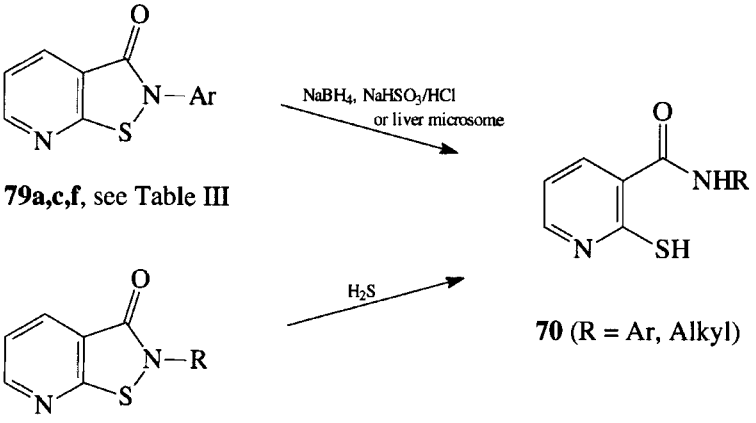
19

20a: $NR_2 = NEt_2$, n = 2 (59%)
20b: NR_2 = Piperidyl, n = 2 (60%)
20c: NR_2 = Piperidyl, n = 3 (60%)
20d: NR_2 = 3-Aza-bicyclo[3.2.2]non-3-yl, n = 2 (68%)
20e: NR_2 = 3-Aza-bicyclo[3.2.2]non-3-yl, n = 4 (83%)

135

SCHEME 53

Reductive ring opening of **79** with $NaBH_4$ [49], $NaHSO_3$ [45] and liver microsomes [49] gives 2-mercapto-3-pyridinecarboxamides **70** at a fairly rapid rate. Those *N*-aryl-pyrido isothiazolones, which have electron-releasing substituents conjugated to the isothiazolone nitrogen (e.g. 4-MeO or 2,4-$(MeO)_2$) or in which the sulfur is sterically shielded (e.g. 2,6-Me_2) underwent reduction less rapidly but were still reduced at an acceptable rate (Scheme 54). The complete conversion of *N*-alkyl isothiazolopyridine-3(2*H*)-ones **8b–g** into the 2-mercapto-3-pyridinecarboxamides **70** (R = alkyl) occurred after treatment with hydrogen sulfide (80–85%) [43d].



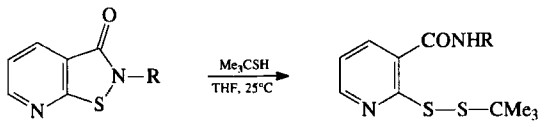
79a,c,f, see Table III

70 (R = Ar, Alkyl)

8b-g, see Table II

SCHEME 54

The reduction of isothiazolones with *tert*-butyl mercaptan provides a useful model for the microsomal reduction [49]. Thus, *tert*-butyl mercaptan reacts with **79** or **84** to form the corresponding ring opened mixed disulfanes **136** and **137** (Scheme 55).



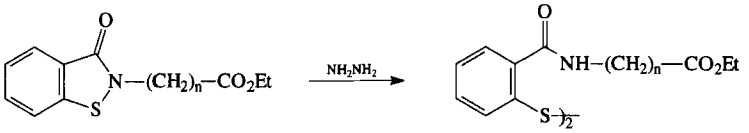
79: R = Ar
84: R = $ArCH_2$

136: R = Ar
137: R = $ArCH_2$

SCHEME 55

It was found that the rate of reaction of isothiazolones **79** with Me_3CSH to form the mixed disulfane **136** was proportional to their rate of reduction by the microsomal preparation to form the thiols **70**. Indeed, all of the benzylic isothiazolones **84** reported in Table V were found to be relatively unreactive towards *tert*-butyl mercaptan [49].

In the reaction of **122** ($n = 1$ and 2) with hydrazine hydrate the products of ring-opening 2,2′-dithiobis[*N*-(ethoxycarbonylmethyl)benzamides] **138** and **139** are formed (Scheme 56).



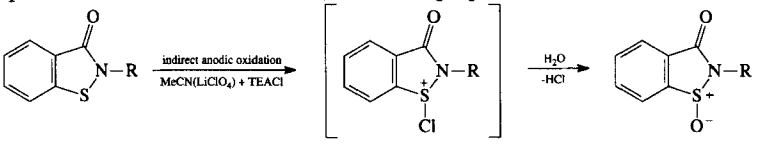
122

138: n = 1
139: n = 2

SCHEME 56

3.3. Oxidations

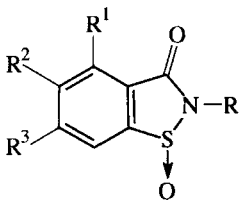
The 1-oxides **140a–i** of 1,2-benzisothiazolones **1**,**2**,**5**, and **6** are synthesized by oxidation with 1 equivalent *meta*-CPBA (**140a**) [48], by photochemical reaction (**140c**) [78], by oxidation of 2,2′-dithiobis(benzamides) with sodium periodate [39], or from 1,3-benzothiazin-4-one with $NaIO_4$ involving ring contraction (**140a** and **140b**$_{1,2}$) (Table VI) [39]. The indirect electrochemical oxidation, in acetonitrile medium of **1a** and **5e**, mediated by chlorine anion, leads to the isolation of the corresponding sulfoxides **140a** and **140c** [80]. These oxidations, occurring in nearly quantitative yields, are attractive alternatives for the preparation of these sulfoxides; see also [75].



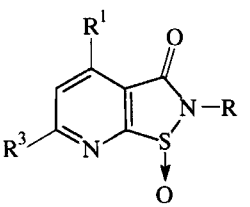
140a: R = H
140c: R = Ph

SCHEME 57

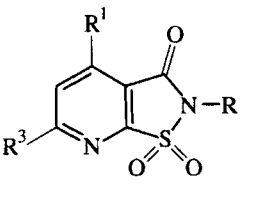
TABLE VI 1,2-Benzisothiazol-3(2*H*)-one 1-oxides **140a–k** and **142a–c** and 1,1-dioxides **143a–k**



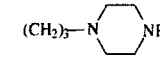
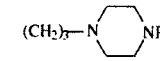
140



142



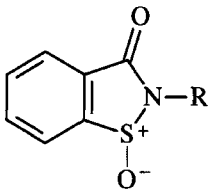
143

Cpd. No.	*R*	*R*^{1}	*R*^{2}	*R*^{3}	*Yield, %*	*Ref.*
140a	H	H	H	H	72,85	[39,48,77]
140b$_1$	H	H	MeO	MeO	90	[39]
140b$_2$	H	H	EtO	EtO	58	[39]
140c	Ph [a]	H	H	H		[48,77,78,79]
140d	MeCO	H	H	H		[7,76]
140e	EtCO	H	H	H		[7,76]
140f	$PhCH_2CO$	H	H	H		[7,76]
140g	$PhSO_2$	H	H	H	65	[7,76]
140h	4-$MeC_6H_4SO_2$	H	H	H		[7,76]
140i	Me_2CH [b]	H	H	H	89	[27]
140j	H	NO_2	H	NO_2	60	[33]
140k	Me	NO_2	H	NO_2	85	[33]
142a	Me	Me	H	Me	84	[46]
142b	4-ClC_6H_4	Me	H	Me	84	[46]
142c	$PhCH_2$	H	H	H	–	[49]
143a	H	Me	H	Me	70	[69]
143b	Me	Me	H	Me	40,75	[46,69]
143c	$PhCH_2$	Me	H	Me	75	[69]
143d	$CH_2CH{=}CH_2$	Me	H	Me	80	[69]
143e	CH_2CO_2Me	Me	H	Me	75	[69]
143f	CH_2COMe	Me	H	Me	65	[69]
143g	CH_2COPh	Me	H	Me	80	[69]
143h	$COCH_3$	Me	H	Me	90	[69]
143i	$(CH_2)_2O$-tosyl	Me	H	Me	–	[68]
143j$_{1-6}$		Me	H	Me	54–74	[68,70]
143k$_{1-5}$		Me	H	Me	46–75	[68,70]

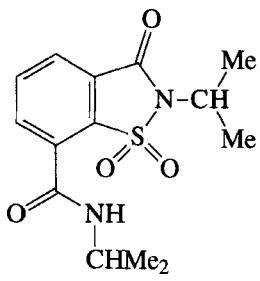
[a]Substituents in 4-position of 2-aryl ring: MeO, Me, Cl, CN, photochemical reaction (8–17%) [78]; [b]7-$CONHCHMe_2$; [c]R^4 = Me, Ph, 3-ClC_6H_4, 3-$CF_3C_6H_4$, 2-pyridyl, 2-pyrimidyl; [d]R^4 = Me, Ph, 2-$MeOC_6H_4$, 2-pyridyl, 2-pyrimidyl.

The electrochemical oxidation of **5e** in acetonitrile ($LiClO_4$) without addition of TEACl was also studied [81].

The chlorination of 2-mercaptobenzoic acid and the condensation with acylamides or arylsulfonamides gives **140d–h** [7,76a,b]. The 1-oxide **140i** was prepared by oxidation of the corresponding 1,2-benzisothiazolone with 30% H_2O_2–AcOH at room temperature. The corresponding 1,1-dioxide **141a** was formed with H_2O_2 at elevated temperatures (Scheme 58) [27].



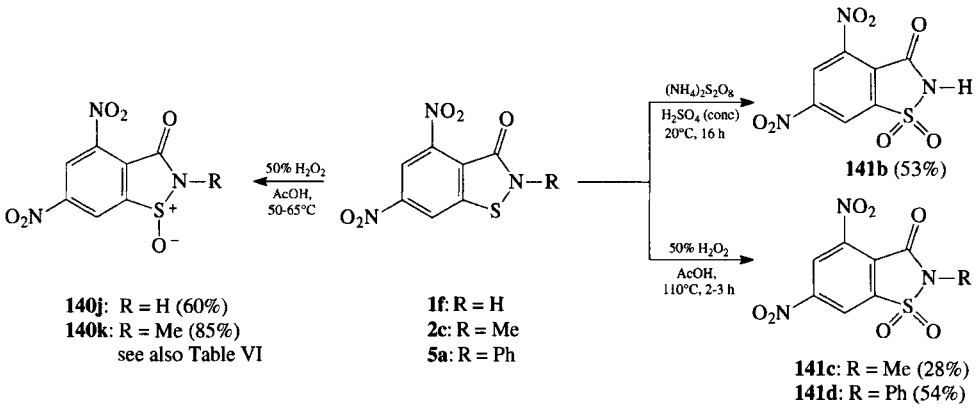
140a-i, see Table VI



141a

SCHEME 58

The reaction of **1f** with 50% H_2O_2 in glacial acetic acid at 50–65°C gave **140j**. Further oxidation did not take place even if the reaction mixture was heated at 100°C for several hours. However, the 1,1-dioxide **141b** (dinitrosaccharine) was obtained with a stronger oxidant such as ammonium persulfate in concentrated H_2SO_4 (Scheme 59) [33].



140j: R = H (60%)
140k: R = Me (85%)
see also Table VI

1f: R = H
2c: R = Me
5a: R = Ph

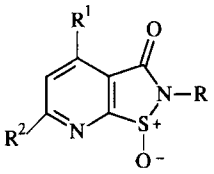
141b (53%)

141c: R = Me (28%)
141d: R = Ph (54%)

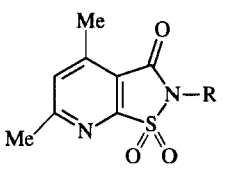
SCHEME 59

Unlike **1f**, 2-methyl-isothiazolone **2c** reacts with 50% H_2O_2 in glacial acetic acid to afford the 1-oxide **140k** or the 1,1-dioxide **141c**, depending on the reaction conditions (Scheme 59). When the reaction was carried out at 50°C, the 1-oxide **140k** was formed in 85% yield. On the other hand, the 1,1-dioxide **141c** was prepared using boiling AcOH (118°C). Compound **5a** reacted with 50% H_2O_2 at 100–110°C to afford the 1,1-dioxide **141d** in 54% yield [33].

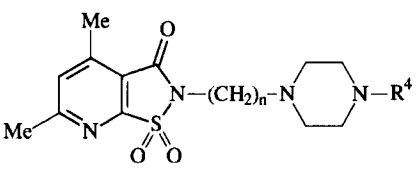
The 1-oxides **142a–c** were prepared by oxidation of the corresponding pyridoisothiazolones with 1.0 equivalent *meta*-CPBA in CH_2Cl_2 at − 10°C (**142a,b**) [46] and at 0°C (**142c**) [49]. The oxidation of **78b** with 2.3 equivalents of *meta*-CPBA in CH_2Cl_2 at − 10°C or 0°C gives **143a** [46] (see Table VI).



142a-c, see Table VI



143a-h: see Table VI



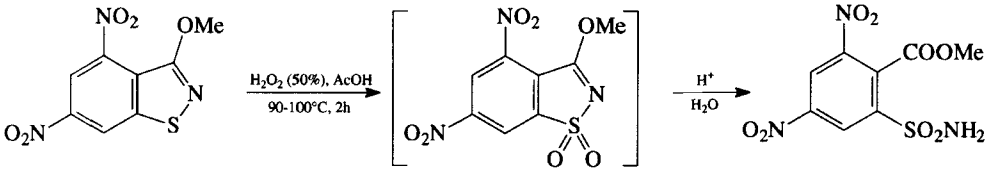
143j $_{1-6}$: R^4= Me, Ph, 3-ClC_6H_4, 3-$CF_3C_6H_4$, 2-Pyridyl, 2-Pyrimidyl; n = 2

143k$_{1-5}$: R^4= Me, Ph, 2-$MeOC_6H_4$, 2-Pyridyl, 2-Pyrimidyl; n = 3

SCHEME 60

The pyridoisothiazolone **78b** was transformed to 1,1-dioxide **143a** via oxidation with $KMnO_4$ (70% yield) [69]. The *N*-substituted derivative **143b–g** of the dioxide **143a** were obtained in good yields (65–80%) via reaction of the sodium salt of **143a** with the appropriate halogeno derivatives, e.g. methyl iodide, benzyl bromide, allyl bromide. A suspension of **143a** in acetic acid was heated and the 2-acetyl derivative **143h** was obtained (Scheme 60) [69]. The piperazinylalkyl derivatives **143k**$_{1-5}$ were prepared in good yields (50–75%) through the action of 4-(3-chloropropyl)-piperazines and **143a** in ethanol in the presence of NaOEt. The synthesis of piperazines **143j**$_{1-6}$ involved the replacement of the tosyl group in **143i** by the corresponding *N*-substituted piperazines [70].

It is known that 1,2-benzisothiazoles are generally much more resistant to oxidation than 1,2-benzisothiazolones [1]. Surprisingly, however, **144** reacted with 50% H_2O_2 in acetic acid at 100°C with ring opening to benzenesulfamide **146** in 84% yield [33]. The reaction probably involves formation of **145** followed by a hydrolytic cleavage of the C=N bond (Scheme 61).



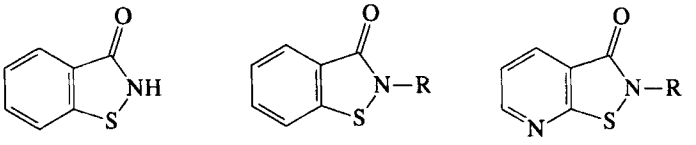
144 **145** **146**

SCHEME 61

4. BIOLOGICAL ACTIVITY AND TOXICITY

1,2-Benzisothiazol-3(2*H*)-ones **1–5** are a group of compounds with a great spectrum of biological activities and the antimicrobial properties have been widely described [1,3,81]. In recent years, the attention has been directed to the synthesis and activity

of bioisosteric derivatives (PITs) in which the benzene ring is replaced by a heterocyclic ring such as pyridine as in compounds **8**,**78**, and **79** (Scheme 62) [47–49].

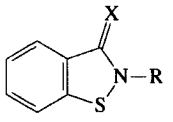


1 (BIT) **2-5** (BITAs) **8**: R = Alkyl
78: R = H
79: R = Aryl
(PITs)

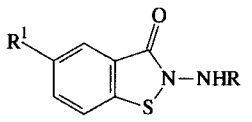
SCHEME 62

A general interest in these compounds shifted to their industrial application as biocides even if the parent compound 1,2-benzisothiazol-3(2*H*)-one **1** (BIT, trade name: Proxel [87]) is not recommended for pharmaceutical and cosmetic preparations since it is a skin sensitizer. The allergic contact potential has been known [82–86]. Stable antimicrobicidal liquid preparations containing 1,2-benzisothiazol-3-ones **1** and **2** are industrial microbiocides [87,88] and are used as fungicides for paints [89–91] and silver halide photographic materials [92–94]. Broad-spectrum industrial bactericides and antiseptics for long-term use at low rates contain 1,2-benzisothiazolone **1a** or its alkali salts and 2-methylisothiazolone at a synergistic ratio [95]. Photodegradation of the biocide **1** (BIT) for protection of stored materials has been discussed [96]. Many other references to the preparation of these compounds exist, mainly in the patent literature.

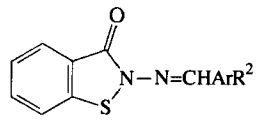
The 2-substituted 1,2-benzisothiazol-3(2*H*)-ones have been reported to show also a variety of biological activities and their antifungal and antibacterial properties have attracted considerable attention [1,8,14]. In this context a number of *N*-(hydroxy alkyl)-1,2-benzisothiazolones **17** [13,14,20], their carbamic esters **21–23** [19–21] and (1,2-benzisothiazolone-2-yl)acetamides [64,65] were demonstrated to have antimicrobial activity. Thus, *N*-hydroxyalkyl derivatives **17** have been claimed to possess *in vitro* antibacterial activity against *Mycobacterium* species [14]. Recently, the interest in 1,2-benzisothiazolones and their corresponding thiono derivatives has increased [13] and the reported antibacterial activities have been evaluated. A series of *N*-(2-hydroxyethyl)-1,2-benzisothiazolone and thiono carbamic esters **17**, **18**, **21**, and **25** have been synthesized and tested against *Mycobacterium avium* strains [19]. Several compounds **17** were active against selected fungi and Gram-positive organisms [13]. Although, it is not possible to state precise relationships between antimicrobial activity and chemical structure, for the studied compounds, a correct balance of the carbamic moiety and lipophilicity seems to be relevant for the antimicrobial action [20]. Few of the tested compounds turned out to have any DNA-damaging properties [20]. Compounds **19** that are substituted by an aminoalkyl group in the 2-position, were potent inhibitors of adenosine diphosphate induced first-phase aggregation, but adverse toxicological results terminated their further development (Scheme 63) [17].



2: R = $CH_2CH(C_2H_5)C_4H_9$, X = O
17: R = $(CH_2)_nOH$, X = O
18: R = $(CH_2)_2OH$, X = S
19: R = $(CH_2)_nNR_2$, X = O
21-23: R = $(CH_2)_nO-CONHR$, X = O
25: R = $(CH_2)_2O-CONHR$, X = S



4: R = H
30: R = Ar

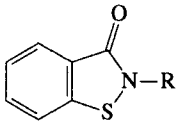


32: R^2= Cl, NO_2, OH, MeO

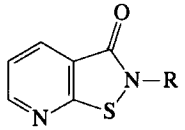
SCHEME 63

The introduction of the 2-amino substituents as well as the 5-methyl substitution on the 1,2-benzisothiazole system were directed to modulate molecular features of the compounds, in particular lipophilicity. The tested 2-amino compounds **4** and **30** show a powerful *in vitro* antiplatelet activity and various modifications resulted in molecules possessing antiaggregation effects as well as spasmolytic actions [24,25]. Correlations between experimental and calculated lipophilic indices of new hydrazones **32** with potential antimicrobial activity were described [26].

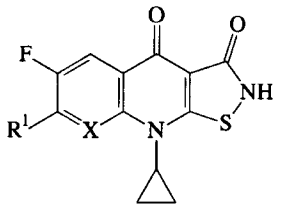
A series of benzoisothiazolones **5** (R = Ar) [48] and heteroaryl-fused 2-arylisothiazolones **79** (R = Ar) [47], 2-(arylmethyl)pyridoisothiazolones **84** ($R = ArCH_2$) [49] and monocyclic 2,5-diarylisothiazolones [97] (see Part I) are reported that inhibit the Il-1β-induced breakdown of bovine nasal septum cartilage in an organ culture assay. These compounds represent novel, nonpeptidic disease-modifying agents for the treatment of arthritic diseases. The pyridoisothiazolones **84** ($R = ArCH_2$) are relatively resistant to reductive metabolism by liver microsomal preparations and appear to inhibit cartilage breakdown by interfering with the proteolytic activation of matrix metalloproteinase (Scheme 64) [49].



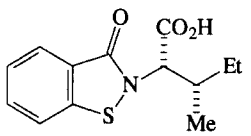
5: R = Ar
27: R = R'$NHSO_2C_6H_4$



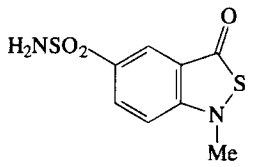
79: R = Ar
84: R = $ArCH_2$



105



147



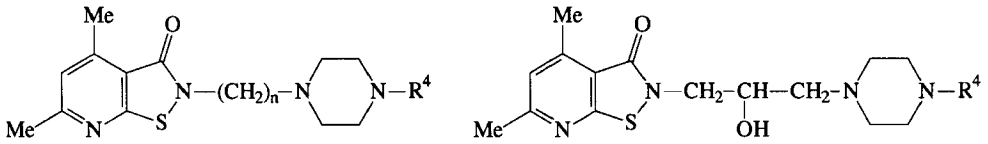
148

SCHEME 64

The sulfonamide derivatives **27** generally exhibit antiviral potency against the nucleocapsid p7 protein (NCp7) zinc finger domains of the human immunodeficiency virus type 1 (HIV-1) [22]. *N*-isoleucyl-benzisothiazolone **147** was characterized as a novel degradation product of 2,2′-dithiobis(*N*-isoleucyl-benzamide) and show also inhibitor activity of HIV nucleocapsid protein zinc fingers [98,99].

9-Cyclopropyl-2,3,4,9-tetrahydroisothiazolo[5,4-*b*]chinoline **105** possesses more potent antibacterial activity than ciprofloxacin [57].

The biologically active *N*-piperazinylalkyl derivatives **127** and **129** were examined to the role of the central alkanyl chain length, the introduction at the central alkanyl chain of an ether oxygen atom or a hydroxyl group, and variation of the 4-substitution of the piperazine ring (Scheme 65) [67–70]. They were synthesized as CNS and antimycobacterial agents.



127a-c: n = 2-4
129: n = 1

127d

SCHEME 65

The 1-benzisothiazolone derivative **148** was found by computer screening for subnanomolar efficient inhibitors of carboanhydrase II (CA II) [100].

5. CONCLUSIONS

1,2-Benzisothiazol-3(2*H*)-ones **1-5** are known to possesses several biological activities, especially antimicrobial functionalities, e.g. *N*-hydroxyalkyl-1,2-benzisothiazolone, its corresponding thione and the corresponding carbamic esters. They are potent industrial microbiocides because of their antifungal and antibacterial properties. The 2-amino-1,2-benzisothiazolone derivatives show powerful antiplatelet activity and spasmolytic actions. The bioisostere 2-aryl- and 2-arylmethyl-pyridoisothiazolones inhibit cartilage breakdown by interfering with the proteolytic activation of matrix metalloproteinases. *N*-piperazinylalkyl-pyridoisothiazolones show antimycobacterial and anorectic activities. 1,2-Benzisothiazolone sulfonamide derivatives exhibit also antiviral activity against the HIV-1 virus.

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