Albert Lévai

Department of Organic Chemistry, Lajos Kossuth University, H-4010 Debrecen, P.O. Box 20, Hungary
Received June 28, 1999

J. Heterocyclic Chem., **37**, 199 (2000).

1. Introduction.

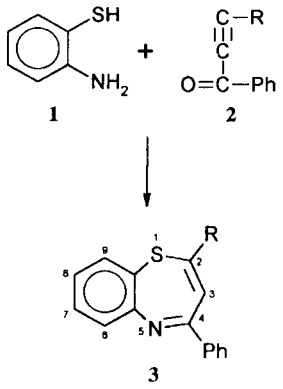
The 1,5-benzothiazepine is one of the three possible benzo-condensed derivatives, *viz.* 1,4-, 4,1- and 1,5-benzothiazepines of the 1,4-thiazepine [1]. The parent 1,5-benzothiazepine itself has not hitherto been described in the literature. However, its derivatives belong to the most frequently studied benzothiazepines. This may be due to their easy availability and the wide range of their bioactivities. Cardiovascular [2], vasodilator [3,4] and antiarrhytmic [5] actions of some 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones have already been published in the early seventies. Later on, haemodynamic effects [6], antiulcer activity [7,8], calcium antagonistic and spasmolytic activities [9-13], angiotensine converting enzyme inhibition [14,15], *etc.* have been described as their major activities. Moreover, antihypertensive drugs with 1,5-benzothiazepine active ingredients have already been marketed. On all these bases, the 1,5-benzothiazepines are useful compounds in the drug research which stimulated the invention of various synthetic procedures for their preparation and chemical transformations.

The major aim of this review article is to provide an account for the most important methods invented for the synthesis of 1,5-benzothiazepines. Chemical transformations utilized mainly to obtain their derivatives of beneficial bioactivities are also discussed with the help of adequate examples.

2. Synthesis of 1,5-Benzothiazepines and 1,5-Benzothiazepin-4(5*H*)-ones.

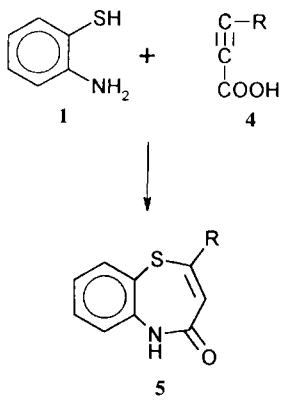
As mentioned previously, the 1,5-benzothiazepine as parent compound, has not yet been described in the literature. However, its 2,4-disubstituted derivatives have already been published. 2-Aminothiophenol (**1**) was allowed to react with alkynones **2** in a mixture of hot methanol and acetic acid to obtain 2,4-disubstituted 1,5-benzothiazepines **3** [16,17] (Scheme 1).

Scheme 1



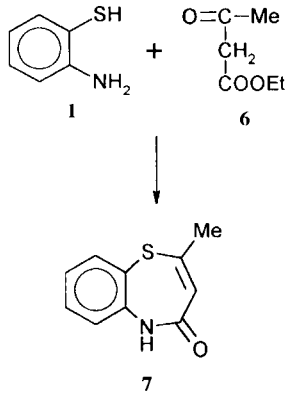
For the synthesis of 1,5-benzothiazepin-4(5*H*)-ones several procedures have hitherto been developed. In the case of a quite general and simple procedure, 2-aminothiophenol (**1**) is heated either with propiolic acid (**4**) (R = H) or its β-substituted derivatives **4** to yield the appropriate 1,5-benzothiazepines **5** [18-20] (Scheme 2).

Scheme 2



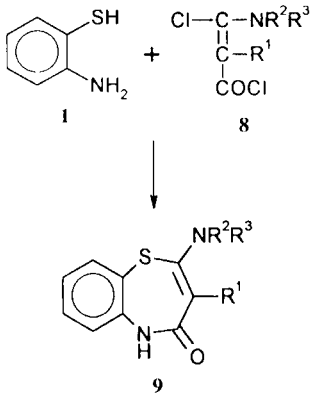
2-Methyl-1,5-benzothiazepin-4(5*H*)-one (**7**) has been prepared by the reaction of 2-aminothiophenol (**1**) with ethyl acetoacetate (**6**) in xylene at reflux temperature [21,22] (Scheme 3).

Scheme 3



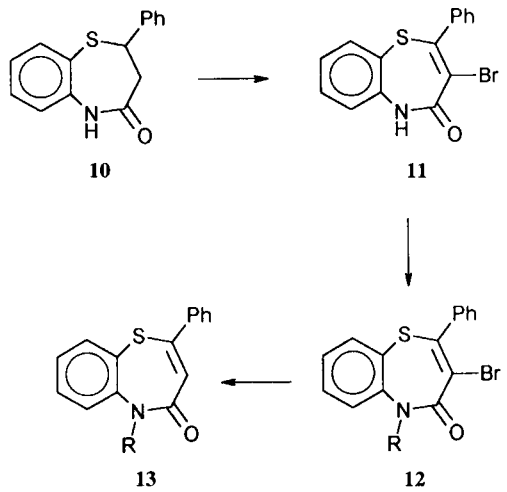
2,3-Disubstituted 1,5-benzothiazepin-4(5*H*)-ones **9** were synthesized by the reaction of 2-aminothiophenol (**1**) with α-chloro-β-chlorocarbonyl enamines **8** in the presence of pyridine [23] (Scheme 4).

Scheme 4



Formerly we have developed a simple and convenient procedure for the preparation of 1,5-benzothiazepin-4(5*H*)-ones **13** by the debromination of 3-bromo-1,5-benzothiazepin-4(5*H*)-ones **12**. 2,3-Dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (**10**) was converted into compound **11** on bromination with *N*-bromosuccinimide [24] which was then *N*-acylated and *N*-alkylated to afford 5-substituted 3-bromo-2-phenyl-1,5-benzothiazepin-4(5*H*)-ones **12**. These 3-bromo derivatives were debrominated by zinc dust in a mixture of hot ethanol and acetic acid to give 2-phenyl-1,5-benzothiazepin-4(5*H*)-ones (**13**) [25] (Scheme 5).

Scheme 5

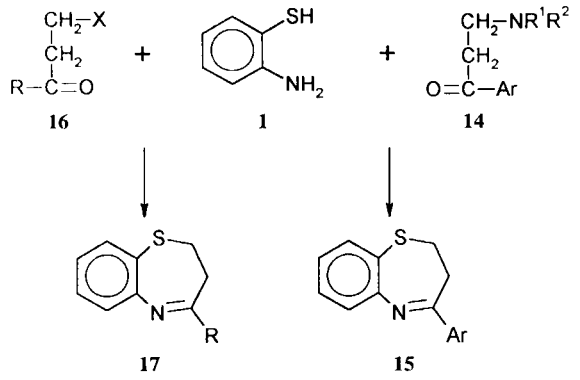


3. Synthesis of 2,3-Dihydro-1,5-benzothiazepines.

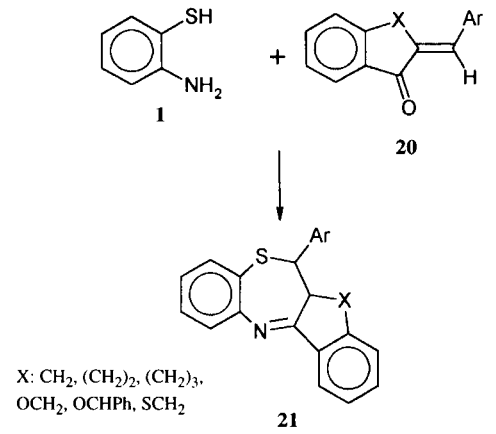
Synthesis and chemical transformations of 2,3-dihydro-1,5-benzothiazepines have been intensely studied by several research groups and as a result, numerous new 1,5-benzothiazepine derivatives have been described in the literature. In our present review article general synthetic procedures and important chemical conversions of benzothiazepines obtained in this way are compiled.

A series of 4-aryl-2,3-dihydro-1,5-benzothiazepines **15** was synthesized by the reaction of 2-aminothiophenol (**1**) with *N,N*-disubstituted (2-aminoethyl)aryl ketones **14** by Hideg and Hankovszky [26-28] (Scheme 6). Similar 4-substituted 2,3-dihydro-1,5-benzothiazepines **17** have been synthesized by the reaction of 2-aminothiophenol (**1**) with β-haloketones **16** [29,30] (Scheme 6).

Scheme 6

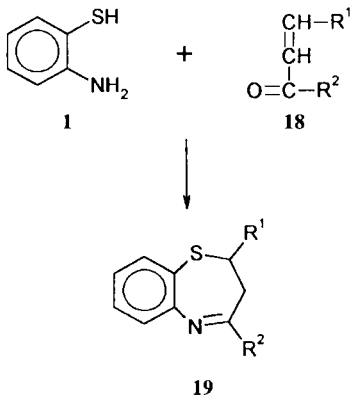


Scheme 8



The 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines **19** (Scheme 7) belong to the most frequently investigated benzothiazepines [21,31-47]. This may be due to the fact that such 1,5-benzothiazepines can easily be synthesized by the reaction of 2-aminothiophenol (**1**) with α,β-unsaturated ketones **18** (Scheme 7). These synthetic procedures have been thoroughly investigated in numerous laboratories. The intense studies resulted in the better understanding of various steric and electronic factors influencing the formation of such 1,5-benzothiazepines.

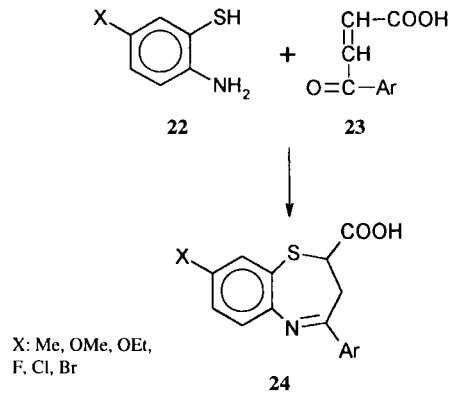
Scheme 7



Similar reaction of exocyclic α,β-unsaturated ketones **20** with 2-aminothiophenol (**1**) afforded tetracyclic benzothiazepines **21** [48-51] (Scheme 8). Stereochemistry of compounds **21** has been elucidated by a combined utilization of various nmr techniques. These spectroscopic measurements unequivocally proved that only one diastereomer was obtained in each case which reveals a completely diastereoselective formation of such benzothiazepines under the reaction conditions used for their synthesis.

To close this paragraph, it should also be mentioned that 4-aryl-2,3-dihydro-1,5-benzothiazepine-2-carboxylic acids **24** have been synthesized in the late eighties by the reaction of 2-aminothiophenols **22** with β-aroylacrylic acids **23** [52,53] (Scheme 9).

Scheme 9



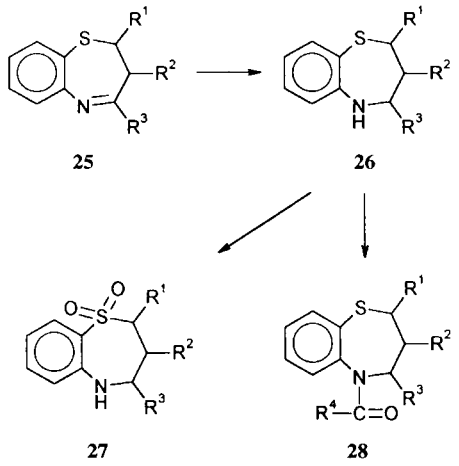
4. Chemical Transformations of 2,3-Dihydro-1,5-benzothiazepines.

4.1. Hydrogenation of the C=N Double Bond.

Hydrogenation of the C=N double bond of the 2,3-dihydro-1,5-benzothiazepines has hitherto received less attention although such tetrahydrobenzothiazepines may be useful intermediates for the synthesis of appropriately substituted complex 1,5-benzothiazepines. Several 4-substituted [27], 2,4-disubstituted [33] and 3,4-disubstituted [28] substances **25** were reduced either by lithium aluminum hydride in hot anhydrous ether or by sodium borohydride in hot ethanol by Hideg and Hankovszky to afford 2,3,4,5-tetrahydro-1,5-benzothiazepines **26** (Scheme 10). Compounds **26** were then converted into their 1,1-dioxides **27** on oxidation with hydrogen peroxide in acetic acid solution at room temperature. Their 5-acyl derivatives **28** have been prepared by *N*-acyla-

tion (Scheme 10). Recently, 2,4-diaryl-2,3,4,5-tetrahydro-1,5-benzothiazepines **26** have been prepared by the hydrogenation of 2,4-diaryl-1,5-benzothiazepines **29** with lithium aluminum hydride by Saturnino *et al.*[54].

Scheme 10

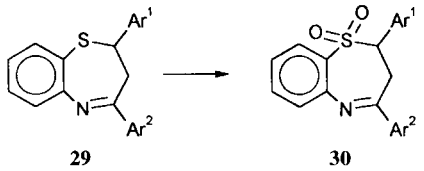


25 **26** **27** **28**

4.2. Synthesis of 2,4-Diaryl-2,3-dihydro-1,5-benzothiazepine 1,1-Dioxides.

According to our knowledge, oxidation of the sulfur atom of the 2,3-dihydro-1,5-benzothiazepines has hitherto been described only in one paper [43]. 2,4-Diaryl-2,3-dihydro-1,5-benzothiazepines **29** were oxidized by hydrogen peroxide in acetic acid at room temperature to obtain 1,1-dioxides **30** (Scheme 11).

Scheme 11

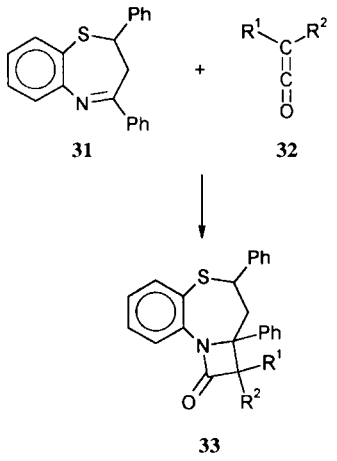


29 **30**

4.3. Preparation of Tricyclic Benzothiazepines by the Cycloaddition Reactions of the C=N Double Bond.

The presence of the polarized C=N double bond of these 1,5-benzothiazepines makes possible the formation of fused ring system by dipolar cycloadditions. In our own study [55] the 2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine (**31**) was allowed to react with *in situ* generated ketenes **32** by the reaction of acid halides and triethylamine and β-lactam derivatives **33** were obtained (Scheme 12). Stereochemistry of compounds **33** has been elucidated by a combined utilization of various nmr techniques.

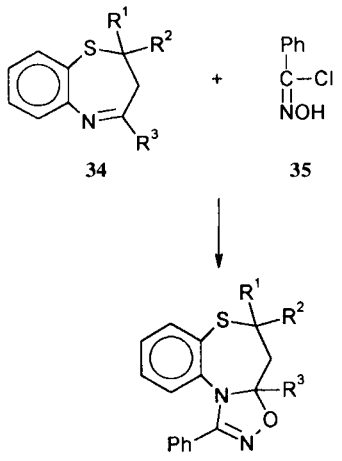
Scheme 12



31 **32** **33**

Chimirri *et al.* [56] synthesized 3a,4-dihydro-1-phenyl-5*H*-[1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepines **36** by the cycloaddition of 2,3-dihydro-1,5-benzothiazepines **34** with benzonitrile oxide generated *in situ* from benzhydroximinoyl chloride (**35**) (Scheme 13).

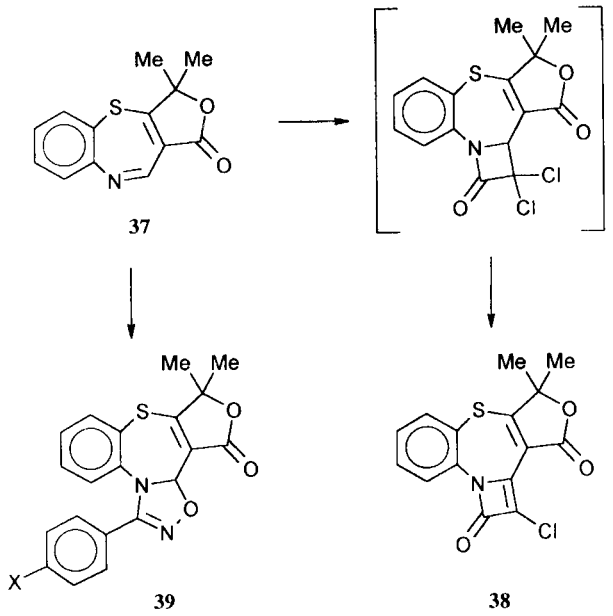
Scheme 13



34 **35** **36**

Similar β-lactam derivatives **38** and [1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepines **39** have also been prepared by the [2 + 2] cycloaddition and 1,3-dipolar cycloaddition of the 3,3-dimethyl-1*H*,3*H*-furo[4,3-*b*][1,5]benzothiazepin-1-one (**37**) [57] (Scheme 14).

Scheme 14

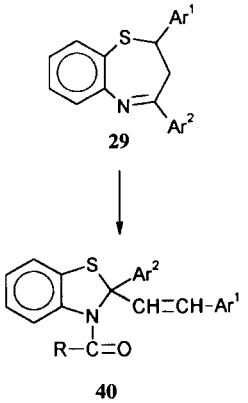


An account on the annelated 1,5-benzothiazepines including β-lactam derivatives has been published by Chimirri *et al.* [58] in 1995.

4.4. Ring Contraction of 2,4-Diaryl-2,3-dihydro-1,5-benzothiazepines.

Some interesting chemical transformations of the benzothiazepines are based on the ring contraction of their seven-membered ring. In our recent study, ring contraction of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines **29** has been performed under acylating conditions to afford 3-acyl-2,3-dihydrobenzothiazoles **40** [59,60]. This simple and convenient procedure renders easily available numerous previously inaccessible 3-acyl-2-aryl-2-(β-arylvinyl)-2,3-dihydrobenzothiazoles **40** (Scheme 15).

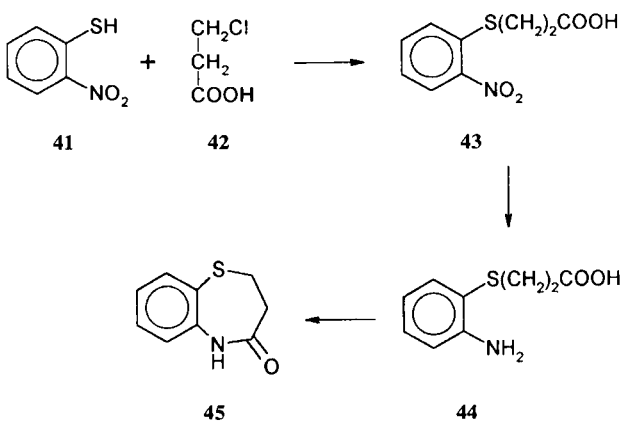
Scheme 15



5. Synthesis of 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones.

The 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones are the most thorougly studied benzothiazepine derivatives. This is mainly due to their numerous important bioactivities. As a consequence, various procedures have been developed for their synthesis. The first synthesis was published as early as 1923 by Mayer and Horst [61]. 2-Nitrothiophenol (**41**) was allowed to react with 3-chloropropionic acid (**42**) to afford nitrocarboxylic acid **43**. Reduction of compound **43** gave aminocarboxylic acid **44** which yielded the target 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**45**) on ring closure (Scheme 16). For the synthesis of the 2-substituted, 3-substituted and 2,3-disubstituted derivatives of compound **45** various methods have been described in the literature.

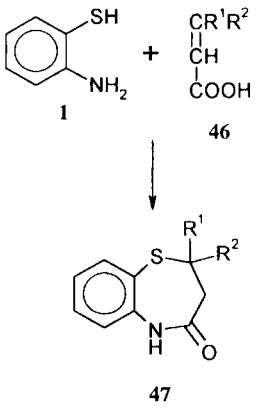
Scheme 16



5.1. Synthesis of 2-Substituted 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones.

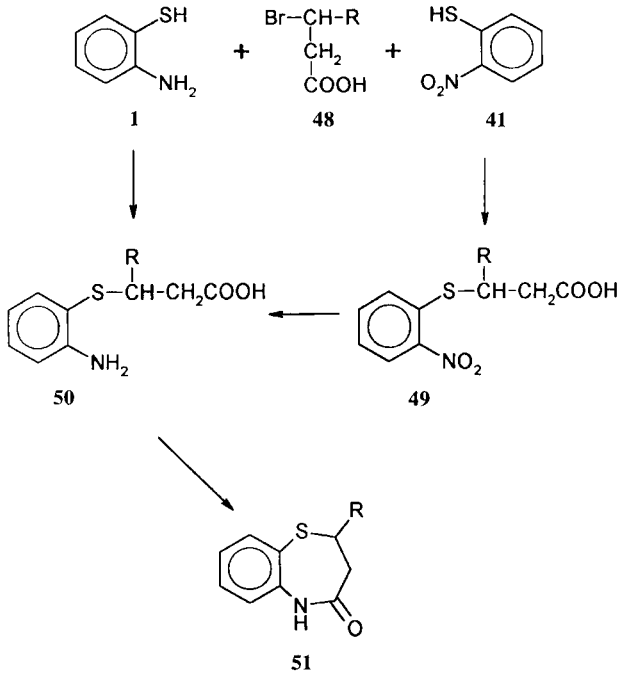
The simplest synthesis is based on the reaction of 2-aminothiophenol (**1**) with α,β-unsaturated carboxylic acids **46**. The first example of this procedure was published by Mills and Whitworth as early as 1927 [62]. Later on, several research groups utilized this convenient method for the synthesis of a wide variety of 2-substituted or 2,2-disubstituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **47** [63-67] (Scheme 17).

Scheme 17



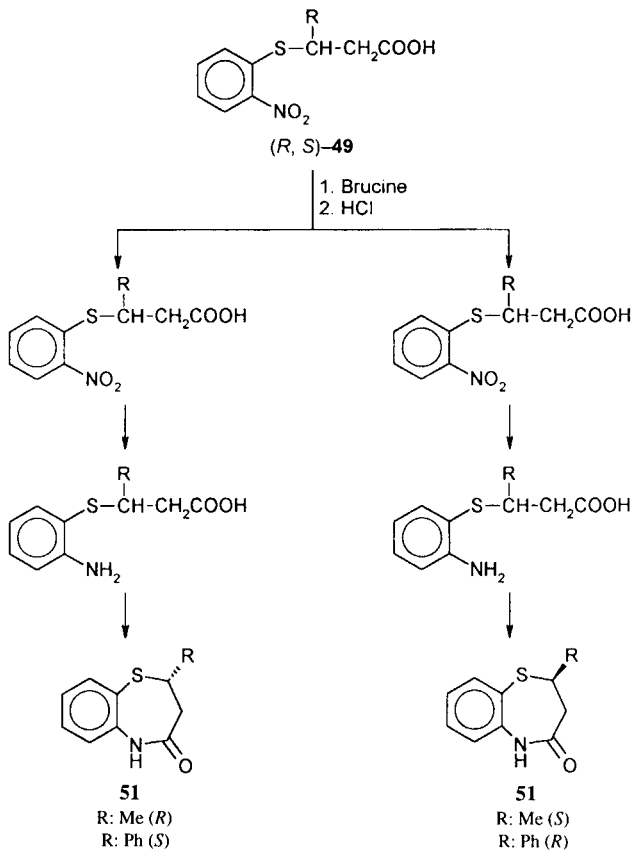
Another convenient procedure starts with the reaction of the 2-aminothiophenol (**1**) or 2-nitrothiophenol (**41**) with 3-bromopropionic acids **48** to afford either nitrocarboxylic acids **49** or aminocarboxylic acids **50**. Reduction of compounds **49** to aminocarboxylic acids **50** followed by ring closure yield the 1,5-benzothiazepines **51** [68] (Scheme 18).

Scheme 18



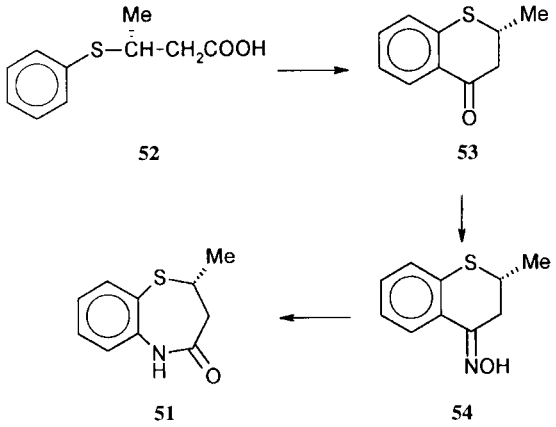
Utilization of this procedure made available an easy preparation of optically active 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones substituted with a methyl or a phenyl group (**51**, R = Me or Ph) at position 2 [69-71] (Scheme 19). Optical resolution of nitrocarboxylic acids **49** by brucine and the decomposition of the brucine salts with hydrochloric acid afforded the optically pure enantiomers of compounds **49**. Reduction of the optically active nitrocarboxylic acids **49** to optically active aminocarboxylic acids **50** followed by their ring closure yielded optically active 2-substituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **51** (Scheme 19). This constitutes the first example for a retrosynthetic preparation of such optically active benzothiazepines.

Scheme 19



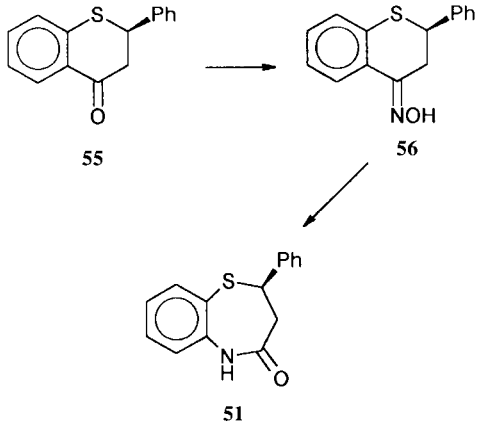
A chemoenzymatic enantioselective synthesis of the (*R*)-2,3-dihydro-2-methyl-1,5-benzothiazepin-4(5*H*)-one ((*R*)-**51**) has been performed by Dike *et al.* [72]. This procedure starts with the Baker's yeast reduction of ethyl acetoacetate. The optically active ester obtained in this way was used for the preparation of the (*R*)-3-(phenylmercapto)butyric acid (**52**) as a key intermediate of this synthesis. Compound **52** was then cyclized into (*R*)-2-methyl-1-thiochromanone (**53**), oxime **54**, of which yielded the (*R*)-2,3-dihydro-2-methyl-1,5-benzothiazepin-4(5*H*)-one ((*R*)-**51**) on Beckmann rearrangement (Scheme 20).

Scheme 20



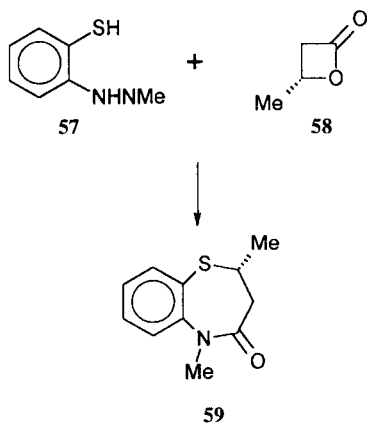
Dike *et al.* [73] managed to work out a similar chemoenzymatic synthesis of the (*R*)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one ((*R*)-**51**) as well. In this case the Baker's yeast reduction of the ethyl benzoyl acetate provided the starting material for a convenient enantioselective synthesis of the (*R*)-1-thioflavanone **55**, oxime **56**, of which was converted into the target optically active 1,5-benzothiazepine (*R*)-**51** on Beckmann rearrangement (Scheme 21).

Scheme 21



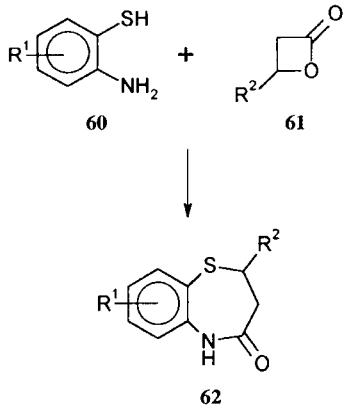
An efficient one-pot synthesis of the (*R*)-2,3-dihydro-2,5-dimethyl-1,5-benzothiazepin-4(5*H*)-one (**59**) has been described by Breitschuh and Seebach [74]. (*S*)-β-Butyrolactone (**58**) was allowed to react with 2-(*N*-methylamino)thiophenol (**57**) to yield compound **59** without the isolation of the appropriate carboxylic acid intermediate (Scheme 22).

Scheme 22



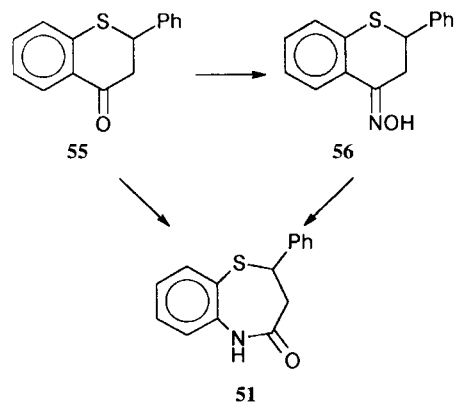
For the synthesis of a large series of 2-substituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **62** similar one-pot procedure has been developed by Ambrogi and Grandolini [75]. 2-Aminothiophenols **60** were allowed to react with β-propiolactones **61** to afford substances **62** without the isolation of the aminocarboxylic acids formed in the first step (Scheme 23).

Scheme 23



As last examples of the procedures developed for the preparation of 2-substituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones, the Schmidt reaction of 1-thiochromanones substituted at position 2 and the Beckmann rearrangement of their oximes should also be mentioned. In our previous studies [76,77], 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (**51**) was obtained either by the Schmidt reaction of the 1-thioflavanone **55** [76] or on the Beckmann rearrangement of its oxime **56** [77] (Scheme 24).

Scheme 24

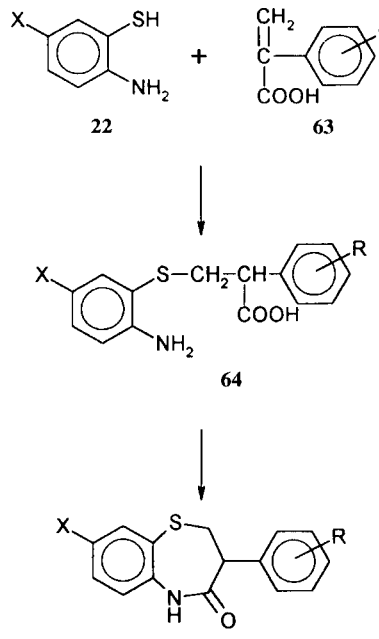


55 56 51

5.2. Synthesis of 3-Substituted 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones.

First representatives of the 3-substituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **59** were synthesized by Carr [78] in 1971. 2-Aminothiophenols **22** were allowed to react with atropic acids **63** to provide β-(2-aminophenylmercapto)hydratropic acids **64** which gave then the target 3-substituted 1,5-benzothiazepines **65** on ring closure with dicyclohexylcarbodiimide (Scheme 25).

Scheme 25

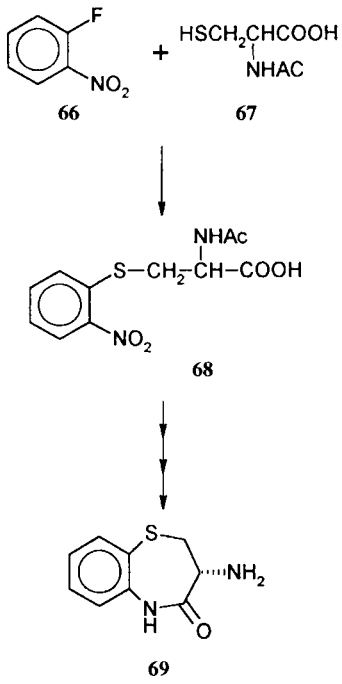


22 63 64 65

X: H, Cl

Optically active 3-amino-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones are very interesting and useful benzothiazepines owing to their angiotensin converting enzyme (ACE) inhibitor activity. The 3-amino-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**69**) was first synthesized by Slade *et al.* [79]. 2-Fluoronitrobenzene (**66**) was allowed to react with *N*-acetylcysteine (**67**) to afford nitrocarboxylic acid **68** which gave then (*R*)-3-amino-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**69**) on several reaction steps (Scheme 26). A wide variety of optically active 3-amino-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones have been synthesized by several research groups [80-84] and the ACE inhibitor activity of these compounds has been emphasized as their major bioactivity.

Scheme 26

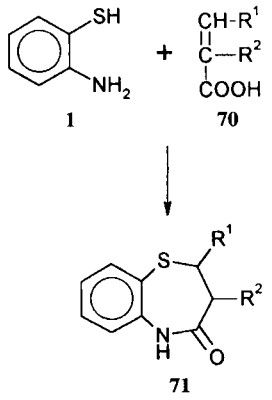


66 67 68 69

5.3. Synthesis of 2,3-Disubstituted 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones.

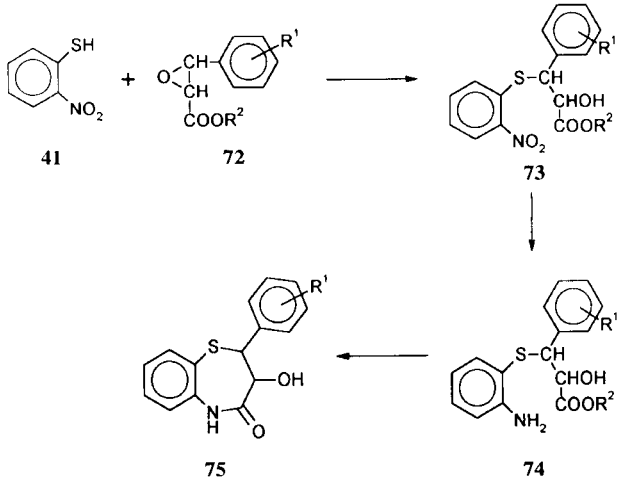
The simplest method for the preparation of 2,3-disubstituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **71** is based on the reaction of 2-aminothiophenol (**1**) with α,β-disubstituted acrylic acids **70** [20,63,65] (Scheme 27). This procedure made possible the preparation of the 2,3-diaryl and 2-aryl-3-alkyl derivatives of these benzothiazepines.

Scheme 27



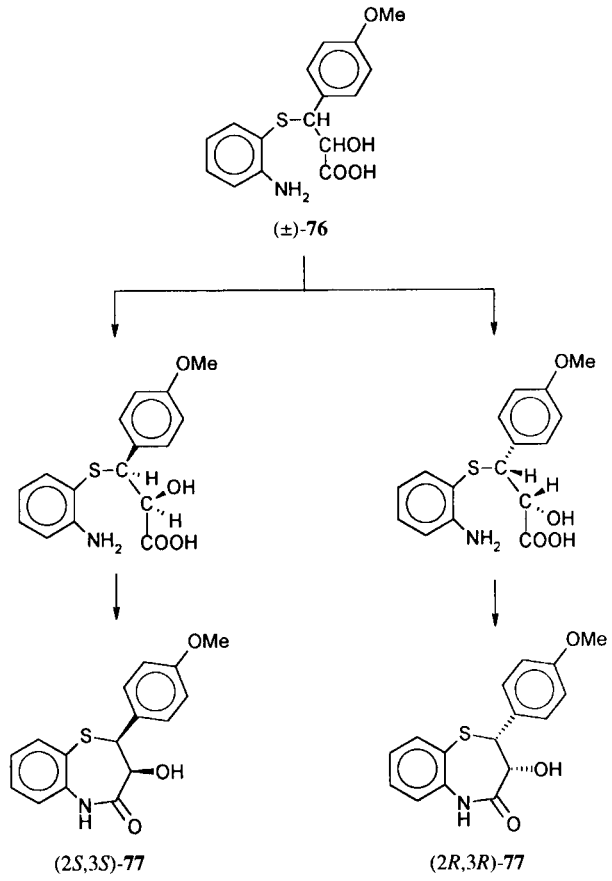
The most frequently studied 1,5-benzothiazepines are the 2-aryl-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5*H*)-ones **75** since some of their optically active derivatives are important antihypertensive agents. For this reason, their synthesis has been investigated by several laboratories and convenient procedures have been developed for their preparation [85-90]. Depending on the reaction conditions, both 2,3-*cis* and 2,3-*trans* diastereomers can be prepared selectively. For their synthesis a general route is illustrated by Scheme 28. 2-Nitrothiophenol (**41**) was allowed to react with phenylglycidic esters **72** to obtain nitrocarboxylic acid esters **73** which were reduced and saponified to afford aminocarboxylic acids **74**. Ring closure of **74** gave 2-aryl-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5*H*)-ones **75** (Scheme 28).

Scheme 28



Synthesis of optically active 2-aryl-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5*H*)-one derivatives is especially important topic of the benzothiazepine chemistry. As a result, wide variety of such compounds has hitherto been published [91-99]. It is not an aim of the present review article to discuss the synthesis, chemical transformations and structure elucidation of such benzothiazepines in detail, we only plan to provide relevant examples to illustrate the major features of the most important synthetic procedures. As an example, Scheme 29 shows the synthesis of the two enantiomers of the *cis*-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (**77**). This multistep procedure starts with the optical resolution of the *cis*-aminocarboxylic acid **76** followed by the ring closure to the benzothiazepine enantiomers. Of course, the *trans*-compounds can be synthesized starting with the optical resolution of the appropriate *trans*-aminocarboxylic or *trans*-nitrocarboxylic acids. This procedure can be considered as the "classical" route for the synthesis of such benzothiazepines.

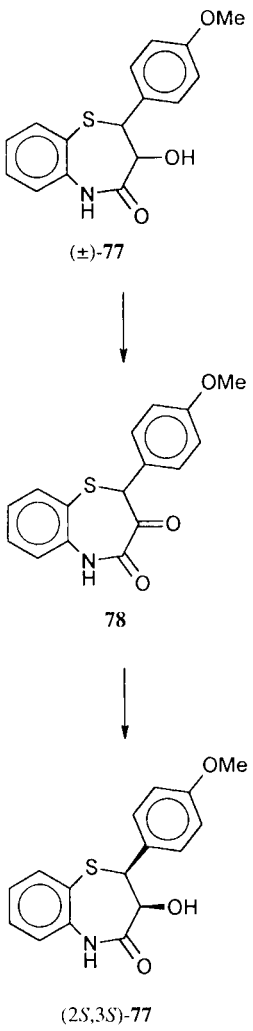
Scheme 29



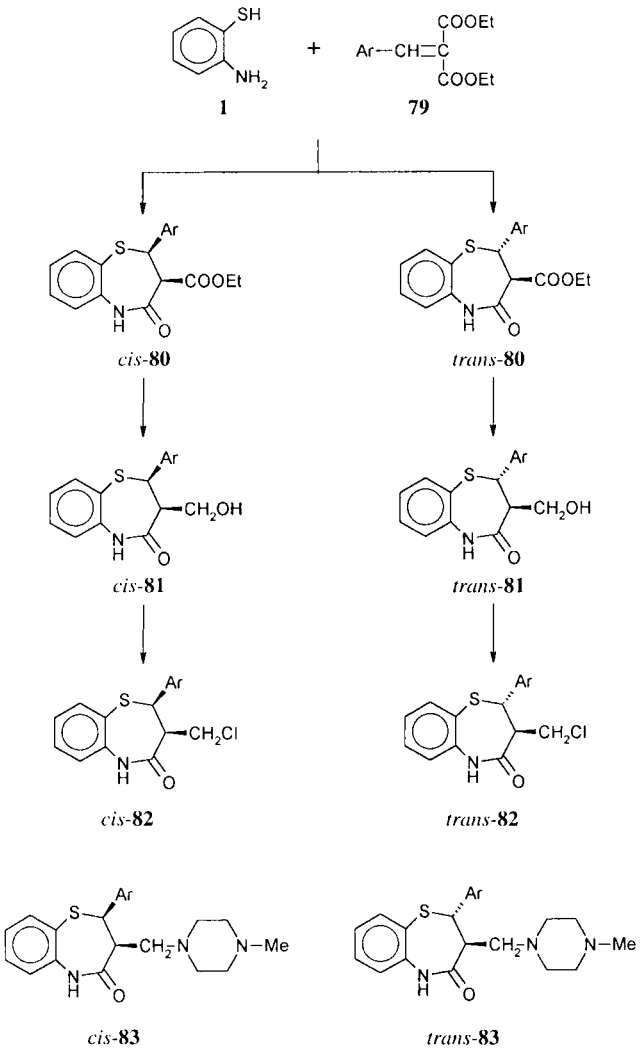
The newest developments concentrate on the preparation of the optically active amino- or nitrocarboxylic acids as key intermediates of the synthesis of the optically active 2-aryl-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5*H*)-ones by the utilization of the most modern procedures. The enzyme-catalyzed kinetic resolution of the racemic hydroxycarboxylic acid belong to this category [100-102]. Various enantioselective synthetic methods have also been utilized to obtain optically active intermediates used for the synthesis of optically active 3-hydroxy-1,5-benzothiazepines [103-109]. (2*S*,3*S*)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (**77**) has also been prepared by the enantioselective reduction of the 2-(4-methoxyphenyl)-1,5-benzothiazepin-3,4(2*H*,5*H*)-dione (**78**) with sodium borohydride and optically active α-amino acids [110] (Scheme 30).

Another interesting group of the 2,3-disubstituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones comprises the ethyl 2-aryl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one-3-carboxylates **80** [7,8,111-113]. Both their *cis*- and *trans*-isomers have been synthesized by the reaction of arylidenemalonates **79** and 2-aminothiophenol (**1**) (Scheme 31). Compounds **80** can then be reduced to alcohols **81** with lithium aluminum hydride in tetrahydrofuran. The alcohols afforded the appropriate chlorides **82** on treatment with thionyl chloride, methanesulfonyl chloride or *p*-toluenesulfonyl chloride. Substances **82** were then heated with *N*-methylpiperazine to obtain 2-aryl-2,3-dihydro-3-(4-methylpiperazinylmethyl)-1,5-benzothiazepin-4(5*H*)-ones **83** (Scheme 31). Some of these benzothiazepines were found to possess considerable antiulcer and gastric inhibitor activities.

Scheme 30



Scheme 31

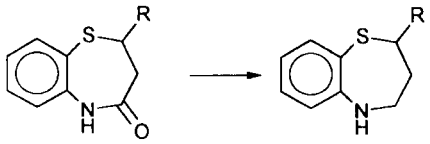


6. Chemical Transformations of the 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones.

6.1. Reduction of the Cyclic Amide Group.

Reduction of the easily available 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones offers an opportunity for the preparation of 2,3,4,5-tetrahydro-1,5-benzothiazepines. However, this efficient chemical transformation has hitherto received little attention. A relatively large series of such tetrahydrobenzothiazepines **84** has been prepared by Krapcho by the reduction of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **51** with lithium aluminum hydride in anhydrous ether [114-116] (Scheme 32). Recently, a tricyclic 1,5-benzothiazepine was reduced by using lithium aluminum hydride under similar reaction conditions [117].

Scheme 32

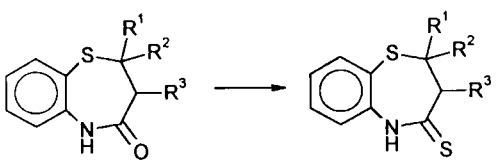


51 **84**

6.2. Conversion of the Amides into Thioamides.

The first example of this conversion has been described by Wilhelm and Schmidt [118] who used phosphorous pentasulfide to convert the 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one into the appropriate thione. Later on, the Lawesson's Reagent [119] was beneficially utilized for the conversion of the 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **85** into the appropriate thiones **86** [67,120-122] (Scheme 33). Some of the thiones obtained by this conversion have also been utilized for the synthesis of new tricyclic benzothiazepines [67,122-129].

Scheme 33

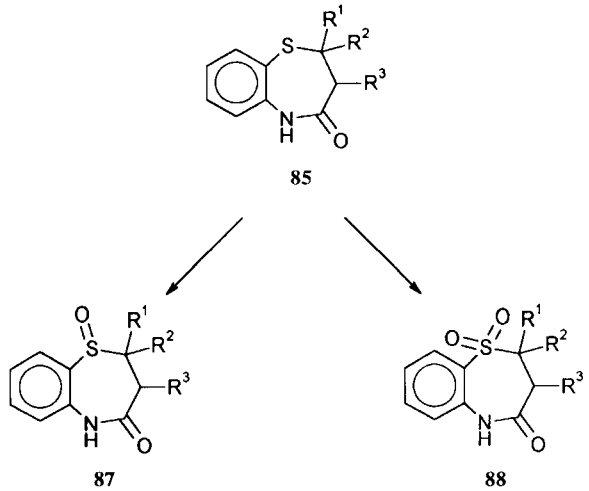


85 **86**

6.3. Oxidation of the Sulfur Atom of the 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones.

Oxidation of the sulfur atom of the 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones has been studied by several research groups and various procedures have been used for the preparation of their sulfoxides and sulfones [62,71,74,79,118,121,130-134]. Sulfoxides **87** have been prepared by using potassium permanganate [62], sodium periodate [79,131], *in situ* generated performic acid [132], *m*-chloroperbenzoic acid [71,121], *tert*-butyl hydroperoxide [74] and dimethyldioxirane [134] (Scheme 34). In the case of the 2-substituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones sulfoxides are obtained as diastereomeric mixtures. However, the application of the dimethyldioxirane as oxidant resulted in high *trans*-diastereoselectivity proved by nmr and X-ray studies [134]. Sulfones **88** have been prepared by hydrogen peroxide [121,130], potassium permanganate [62], *m*-chloroperbenzoic acid [79,118,131] and dimethyldioxirane [134] (Scheme 34).

Scheme 34



85

87 **88**

6.4. *N*-Acylation and *N*-Alkylation of 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones.

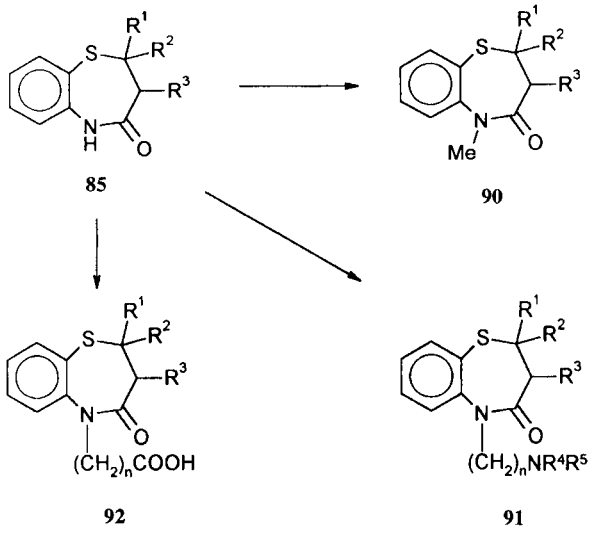
N-Acylation of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **78** has been performed under various reaction conditions to afford the appropriate *N*-acyl derivatives **89** (Scheme 35). 5-Acetyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones have been prepared by using acetic anhydride together with acetic acid [30,66], with anhydrous pyridine [121] or acetic anhydride alone [135]. Utilization of isopropenyl acetate as source of acetyl group with *p*-toluenesulfonic acid has also been described. Other 5-acyl derivatives **89** have been prepared by acylation with acyl chlorides [136].

Scheme 35

85 89

N-Alkylation of the 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones is the most frequently investigated chemical transformation of these 1,5-benzothiazepines. Simple 5-methyl derivatives **90** can easily be prepared by the methylation of compounds **85** with methyl iodide in anhydrous dimethylsulfoxide or dimethylformamide in the presence of sodium hydride [86,121,135] (Scheme 36). Their *N*-alkylamino derivatives **91** have been prepared by *N*-alkylation with aminoalkyl halides in anhydrous toluene in the presence of sodamide [20,63], in dioxane or in dimethylformamide in the presence of sodium hydride [87,92] or in acetone in the presence of potassium carbonate. These 5-(aminoalkyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones belong to benzothiazepines of highest bioactivities and, therefore, they are valuable substances in the drug research. Their most potent member is the *diltiazem* which has already been marketed as an antihypertensive drug [9].

Scheme 36



85 90 92 91

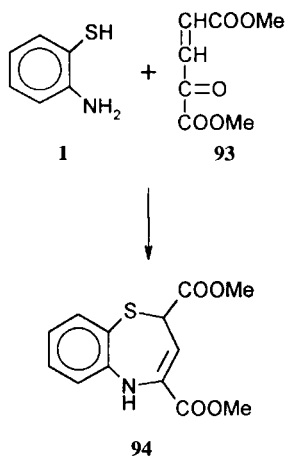
Carboxylic acid derivatives **92** of the 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones have also been synthesized by the *N*-alkylation of the appropriate starting materials [64,65,138,139] (Scheme 36). As alkylating agent, halogenated carboxylic acids or their esters and β-propiolactone, respectively, can be used in anhydrous dimethylformamide in the presence of sodium hydride or potassium *tert*-butoxide.

To close this paragraph, it should also be mentioned that *N*-arylation of such 1,5-benzothiazepines has also been published by Ried and Sell [140].

7. Miscellaneous.

The 2,3-dihydro-1,5-benzothiazepines (*vide supra*) are well known benzothiazepine derivatives. However, the other dihydro-1,5-benzothiazepines has hitherto received less attention. Recently, as an example of such benzothiazepines, dimethyl 2,5-dihydro-1,5-benzothiazepin-2,4-dicarboxylate **94** has been synthesized by the reaction of 2-aminothiophenol (**1**) with dimethyl *E*-2-oxoglutaconate **93** in methanol [141] (Scheme 37).

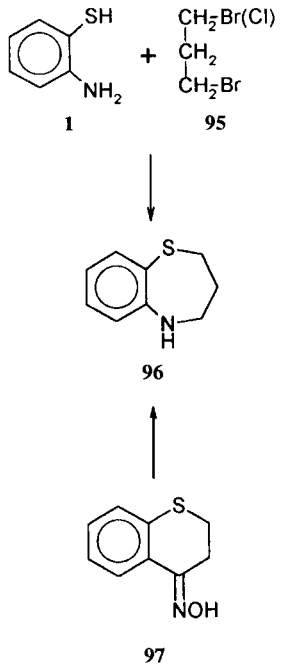
Scheme 37



1 93 94

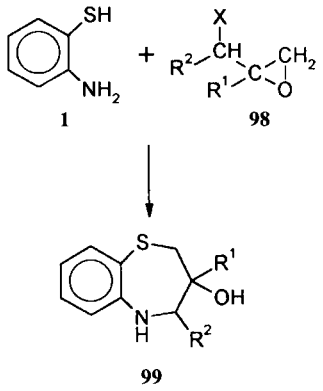
In the previous paragraphs of this review article, the preparation of 2,3,4,5-tetrahydro-1,5-benzothiazepines has already been discussed. It has been shown that such benzothiazepines can be prepared either by the hydrogenation of 2,3-dihydro-1,5-benzothiazepines (*cf.* Scheme 10) or by the reduction of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones (*cf.* Scheme 32). The 2,3,4,5-tetrahydro-1,5-benzothiazepine (**96**) can also be synthesized "directly" by the reaction of 2-aminothiophenol (**1**) with 1,3-dihalopropanes **95** or by the reduction of 1-thiochromanone oxime **97** with lithium aluminum hydride [144] (Scheme 38).

Scheme 38



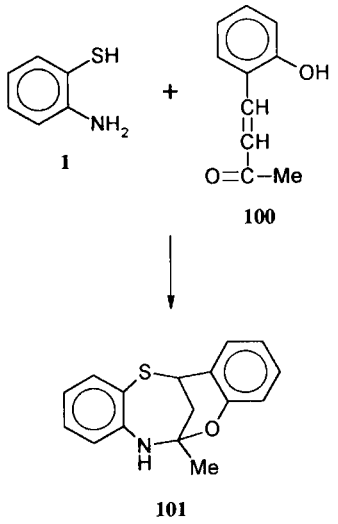
3-Hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepines **99** have been synthesized by the reaction of 2-aminothiophenol (**1**) with 2-(1-haloalkyl)oxiranes **98** [145] (Scheme 39).

Scheme 39



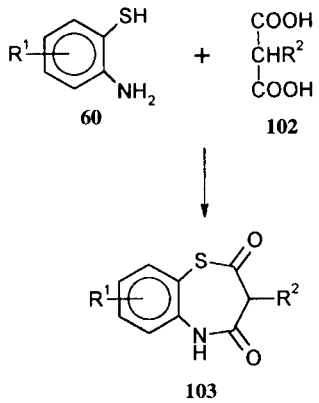
An interesting bridged 2,3,4,5-tetrahydro-1,5-benzothiazepine derivative **101** was described by Svetlik *et al.* [146]. This previously unprecedented benzothiazepine **101** has been synthesized by the cyclocondensation of 2-aminothiophenol with 4-(2-hydroxyphenyl)-3-buten-2-one (**100**) in hot methanol in the presence of concentrated hydrochloric acid (Scheme 40).

Scheme 40



1,5-Benzothiazepin-2,4(3*H*,5*H*)-diones **103** have been synthesized by Ried and Sell [147,148] by the reaction of 2-aminothiophenols **60** with malonic acids **102** in the presence of dicyclohexylcarbodiimide (Scheme 41).

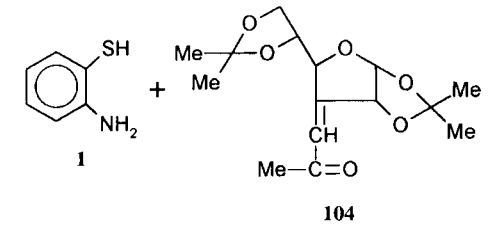
Scheme 41



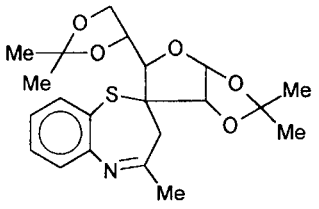
Probably the most unique 1,5-benzothiazepines are their sugar-containing derivatives. Tronchet and Gentile [149] synthesized spirobenzothiazepine **105** by the reaction of 2-aminothiophenol (**1**) with sugar enone **104** in methanol (Scheme 42).

Ito *et al.* [150] synthesized sugar-containing 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one **107** by the reaction of 2-aminothiophenol (**1**) with 5-hydroxy-5-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl)furan-2(5*H*)-one (**106**) in chloroform. Compound **107** was then dehydrogenated to obtain 1,5-benzothiazepin-4(5*H*)-one **108** (Scheme 43).

Scheme 42

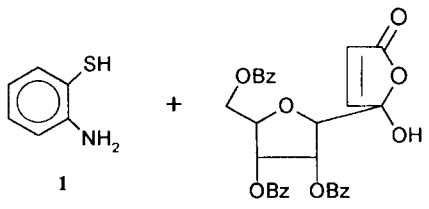


1 104

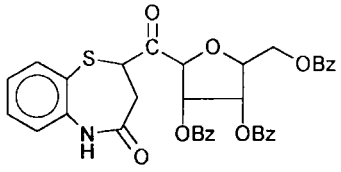


105

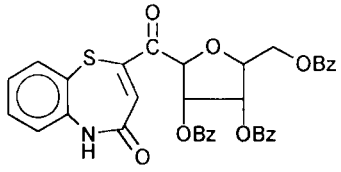
Scheme 43



1 106



107



108

In summary, in our present review article most of the synthetic procedures developed for the preparation and chemical transformations of 1,5-benzothiazepines have been compiled and discussed. Literature data published till June 1999 have been included as references to help the reader to find the original publication concerning an actual synthetic method.

Acknowledgement.

The preparation of this review article was sponsored by the Hungarian National Research Foundation (Grant No. OTKA T029171) for which our gratitude is expressed.

REFERENCES AND NOTES

[*] The survey of the literature was covered until June 1999.

[1] A. Lévai, *Trends Heterocyclic Chem.*, **4**, 51 (1995).

[2] M. Sato, T. Nagao, I. Yamaguchi, H. Nakajima and A. Kiyomoto, *Arzneim.-Forsch.(Drug Res.)*, **21**, 1338 (1971).

[3] T. Nagao, H. Nakajima and A. Kiyomoto, *Japan J. Pharmacol.*, **22**, 1 (1972).

[4] T. Nagao, M. Sato, H. Nakajima and A. Kiyomoto, *Chem. Pharm. Bull.*, **21**, 92 (1973).

[5] K. Yamada, T. Shimamura and H. Nakajima, *Japan J. Pharmacol.*, **23**, 321 (1973).

[6] R. Kusukawa, M. Kinoshita, Y. Shimono, G. Tomonaga and T. Hoshino, *Arznem.-Forsch.(Drug Res.)*, **27**, 878 (1977).

[7] H. Yamamoto and H. Asai, *Chem. Pharm. Bull.*, **34**, 3844 (1986).

[8] T. Asano, T. Okumura, K. Hirano, T. Adachi and M. Sugiura, *Chem. Pharm. Bull.*, **34**, 4238 (1986).

[9] M. J. Kendall and J. V. Okopski, *J. Clin. Hospital Pharm.*, **11**, 159 (1986).

[10] H. Narita, S. Murata, H. Yabana, K. Kikkawa, Y. Sugawara, Y. Akimoto and T. Nagao, *Arzneim.-Forsch.(Drug Res.)*, **38**, 515 (1988).

[11] S. Murata, K. Kikkawa, H. Yabana and T. Nagao, *Arzneim.-Forsch.(Drug Res.)*, **38**, 521 (1988).

[12] K. Kikkawa, S. Murata and T. Nagao, *Arzneim.-Forsch. (Drug Res.)*, **38**, 526 (1988).

[13] H. Narita, M. Gaino, T. Suzuki, H. Kurosawa, H. Inoue and T. Nagao, *Chem. Pharm. Bull.*, **38**, 407 (1990).

[14] Y. Inada, K. Itoh, K. Kamiya, H. Sugihara and K. Nishikawa, *Japan J. Pharmacol.*, **47**, 135 (1988).

[15] K. Itoh, M. Kori, Y. Inada, K. Nishikawa, Y. Kawamatsu and H. Sugihara, *Chem. Pharm. Bull.*, **34**, 1128, 2078, 3747 (1986).

[16] W. Ried and E. König, *Liebigs Ann. Chem.*, **755**, 24 (1972).

[17] A. S. Nahmanovits, T. E. Glomova, G. G. Skrovtsova, T. N. Komarova, B. I. Skrobogatova and U. A. Mansurov, *Izv. Akad. Nauk. SSSR Ser. Khim.*, 1371 (1982).

[18] V. I. Avramenko, V. S. Fedorenko, Z. F. Sholomko and N. Ya., Bozhanova, *Khim. Geterotsikl. Soedin.*, 1049 (1978).

[19] J. Rokach and P. Hamel, *J. Chem. Soc., Chem. Commun.*, 786 (1979).

[20] J. Krapcho and C. F. Turk, *J. Med. Chem.*, **9**, 191 (1966).

[21] W. Ried and W. Marx, *Chem. Ber.*, **90**, 2683 (1957).

[22] A. K. Gupta and U. C. Pant, *Indian J. Chem.*, **20B**, 157 (1981).

[23] R. Buyle and H. G. Viehe, *Tetrahedron*, **25**, 3453 (1969).

[24] J. Krapcho and C. F. Turk, *U.S. Patent* 3,983,106 (1976); *Chem. Abstr.*, **86**, 72716 (1977).

[25] A. Lévai and Gy. Bata, *Acta Chim. Acad. Sci. Hung.*, **99**, 331 (1979).

[26] K. Hideg and O. Hankovszky, *Acta Chim. Acad. Sci. Hung.*, **50**, 403 (1966).
[27] K. Hideg and O. Hankovszky, *Acta Chim. Acad. Sci. Hung.*, **56**, 405 (1968).
[28] K. Hideg and O. Hankovszky, *Acta Chim. Acad. Sci. Hung.*, **75**, 137 (1973).
[29] L. K. Muskalo, *Zh. Obshch. Khim.*, **28**, 742 (1958).
[30] J. C. Lancelot, B. Letois, C. Saturnino and M. Robba, *Synth. Commun.*, **21**, 1901 (1991).
[31] L. K. Muskalo, *Zh. Oshch. Khim.*, **28**, 507 (1958).
[32] W. D. Stephens and L. Field, *J. Org. Chem.*, **24**, 1576 (1959).
[33] O. Hideg-Hankovszky and K. Hideg, *Acta Chim. Acad. Sci. Hung.*, **68**, 403 (1971).
[34] A. Lévai and R. Bognár, *Acta Chim. Acad. Sci. Hung.*, **88**, 293 (1976).
[35] A. Lévai and R. Bognár, *Acta Chim. Acad. Sci. Hung.*, **92**, 415 (1977).
[36] A. Lévai, *Pharmazie*, **34**, 439 (1979).
[37] A. Lévai, R. Bognár and J. Kajtár, *Acta Chim. Acad. Sci. Hung.*, **103**, 27 (1980).
[38] H. Voigt, *Z. Chem.*, **21**, 102 (1980).
[39] A. Lévai, *Pharmazie*, **36**, 449 (1981).
[40] R. A. Mane and D. B. Ingle, *Indian J. Chem.*, **21B**, 973 (1982).
[41] V. D. Orlov, N. N. Kolos and N. N. Ruzhinckaya, *Khim. Geterotsikl. Soedin.*, 1638 (1983).
[42] G. Tóth, Á. Szöllősy, L. Schultz and A. Lévai, *Acta Chim. Acad. Sci. Hung.*, **112**, 167 (1983).
[43] K. P. Jadhav and D. B. Ingle, *Indian J. Chem.*, **22B**, 180 (1983).
[44] A. K. Gupta, V. K. Singh and U. C. Pant, *Indian J. Chem.*, **22B**, 1057 (1983).
[45] U. C. Pant, B. A. Gaur and M Chug, *Indian J. Chem.*, **27B**, 189, 752 (1988).
[46] A. Lévai, *Pharmazie*, **44**, 317 (1989).
[47] A. Lévai, *Heterocyclic Commun.*, **5**, 359 (1999).
[48] G. Tóth, Á. Szöllősy, A. Lévai and H. Duddeck, *Org. Magn. Reson.*, **20**, 133 (1982).
[49] G. Tóth, Á. Szöllősy, A. Lévai and H. Duddeck, *Magy. Kém. Foly.*, **89**, 274 (1983).
[50] A. Lévai, *Sci. Pharm.*, **64**, 523 (1996).
[51] A. Lévai, *Heterocyclic Commun.*, **3**, 211 (1997).
[52] U. C. Pant, B. A. Gaur and M. Chug, *Indian J. Chem.*, **26B**, 947 (1987).
[53] U. C. Pant and M. Chug, *Indian J. Chem.*, **28B**, 435 (1989).
[54] C. Saturnino, P. Saturnino, G. DeMartino, J. C. Lancelot, D. Perrine, S. Rault, M. Robba and F. Rossi, *Il Farmaco*, **52**, 183 (1997).
[55] Á. Szöllősy, G. Kotovych, G. Tóth and A. Lévai, *Can. J. Chem.*, **66**, 279 (1988).
[56] A. Chimirri, R. Gitto, S. Grasso, P. Monforte and M. Zappala, *Heterocycles*, **38**, 2289 (1994).
[57] K. Matsuo, M. Sunago, N. Okutani, T. Takagi, H. Nakamoto and M. Kobayashi, *Chem. Pharm. Bull.*, **43**, 1643 (1995).
[58] A. Chimirri, R. Gitto, S. Grasso, A. M. Monforte and M. Zappala, *Adv. Heterocyclic Chem.*, **63**, 61 (1995).
[59] G. Tóth, A. Lévai, B. Balázs and A. Simon, *Liebigs Ann./Recueil*, 995 (1997).
[60] A. Lévai, *Monatsh. Chem.*, **129**, 909 (1998).
[61] F. Mayer and C. Horst, *Ber. Dtsch. Chem. Ges.*, **56**, 1415 (1923).
[62] W. H. Mills and J. B. Whitworth, *J. Chem. Soc.*, 2738 (1927).
[63] J. Krapcho, E. R. Spitzmiller and C. F. Turk, *J. Med. Chem.*, **6**, 544 (1963).
[64] A. Lévai, *Pharmazie*, **35**, 680 (1980).
[65] A. Lévai and H. Duddeck, *Pharmazie*, **38**, 827 (1983).
[66] J. C. Lancelot, B. Letois , C. Saturnino, P. DeCaprariis and M. Robba, *Org. Prep. Proced. Int.*, **24**, 204 (1992).
[67] V. Ambrogi, A. Giampietri, G. Grandolini, L. Perioli, M. Ricci and L. Tuttobello, *Arch. Pharm.(Weinheim)*, **325**, 569 (1992).
[68] A. Lévai and G. Puzicha, *Synth. Commun.*, **15**, 623 (1985).
[69] G. Puzicha, A. Lévai and L. Szilágyi, *Monatsh. Chem.*, **119**, 933 (1988).
[70] M. Cieczanowicz-Rutkowska, J. Grochowski, A. Lévai, G. Puzicha, P. Serda and G. Snatzke, *Monatsh. Chem.*, **120**, 981 (1989).
[71] G. Puzicha, A. Lévai and G. Snatzke, *Monatsh. Chem.*, **121**, 293 (1990).
[72] S. Y. Dike, D. H. Ner and A. Kumar, *Synlett*, 443 (1991).
[73] S. Y. Dike, D. H. Ner and A. Kumar, *Bioorg. Med. Chem. Letters*, **1**, 383 (1991).
[74] R. Breitschuh and D. Seebach, *Synthesis*, 1170 (1992).
[75] V. Ambrogi and G. Grandolini, *Synthesis*, 724 (1987).
[76] A. Lévai, *Acta Chim. Acad. Sci. Hung.*, **104**, 385 (1980).
[77] A. Lévai, *Acta Chim. Acad. Sci. Hung.*, **107**, 361 (1981).
[78] J. B. Carr, *J. Heterocyclic Chem.*, **8**, 511 (1971).
[79] J. Slade, J. L. Stanton, D. Ben-David and G. C. Mazzenga, *J. Med. Chem.*, **28**, 1517 (1985).
[80] K. Itoh, M. Kori, Y. Inada, K. Nishikawa, Y. Kawamatsu and H. Sugihara, *Chem. Pharm. Bull.*, **34**, 1128, 2078, 3747 (1986).
[81] M. Kori, K. Itoh and H. Sugihara, *Chem. Pharm. Bull.*, **35**, 2319 (1987).
[82] T. Erker and H. Bartsch, *Liebigs Ann. Chem.*, 403 (1992).
[83] J. A. Robl, L. M. Simpkins, J. Stevenson, C.-Q. Sun, N. Murugesan, J. C. Barrish, M. M. Asaad, J. E. Bird, T. R. Schaeffer, N. C. Trippodo, E. W. Petrillo and D. S. Karanewsky, *Bioorg. Med. Chem. Letters*, **4**, 1789 (1994).
[84] J. Das, J. A. Robl, J. A. Reid, C.-Q. Sun, R. N. Misra, B. R. Brown, D. E. Ryono, M. M. Asaad, J. E. Bird, N. C. Trippodo, E. W. Petrillo and D. S. Karanewsky, *Bioorg. Med. Chem. Letters*, **4**, 2193 (1994).
[85] H. Kugita, H. Inoue, M. Ikezaki and S. Takeo, *Chem. Pharm. Bull.*, **18**, 2028 (1970).
[86] H. Kugita, H. Inoue, M. Ikezaki, M. Konda and S. Takeo, *Chem. Pharm. Bull.*, **18**, 2284 (1970).
[87] H. Kugita, H. Inoue, M. Ikezaki, M. Konda and S. Takeo, *Chem. Pharm. Bull.*, **19**, 595 (1971).
[88] T. Hashiyama, H. Inoue, M. Konda and M. Takeda, *J. Chem. Soc., Perkin Trans. 1*, 1725 (1984).
[89] T. Hashiyama, H. Inoue, M. Takeda, K. Aoe and K. Kotera, *J. Chem. Soc., Perkin Trans. 1*, 421 (1985).
[90] T. Hashiyama, H. Inoue, M. Konda and M. Takeda, *Chem. Pharm Bull.*, **33**, 1256 (1985).
[91] H. Inoue, S. Takeo, M. Kawazu and H. Kugita, *Yakugaku Zasshi*, **93**, 729 (1973).
[92] B. Kojic-Prodic, Z. Ruzic-Toros, V. Sunjic, E. Decorte and F. Moimas, *Helv. Chim. Acta*, **67**, 916 (1984).
[93] M. Senuma, M. Shibazaki, S. Nishimoto, K. Shibata, K. Okamura and T. Date, *Chem. Pharm. Bull.*, **37**, 3204 (1989).
[94] T. Gizur, K. Harsányi and E. Fogassy, *J. Prakt. Chem.*, **336**, 628 (1994).
[95] R. Glaser and B. Sklarz, *J. Chem. Soc., Perkin Trans. 2*, 1031 (1989).
[96] J. Gawronski, W. Babs and G. Grynkiewicz, *Polish. J. Chem.*, **65**, 1095 (1991).
[97] C. Giordano, A. Restelli, M. Villa and R. Annunziata, *J. Org. Chem.*, **56**, 2270 (1991).
[98] K. Marthi, S. Larsen, M. Ács and M. Fogassy, *Acta Chem. Scand.*, **50**, 899 (1996).
[99] K. Marthi, S. Larsen, M. Ács, Zs. Jászay and E. Fogassy, *Acta Chem. Scand.*, **50**, 906 (1996).
[100] A. Schwarz, P. B. Madan, E. Mohácsi, J. P. O'Brien, L. J. Todaro and D. L. Coffen, *J. Org. Chem.*, **57**, 851 (1992).
[101] L. T. Kanerva and O. Sundholm, *J. Chem. Soc., Perkin Trans. 1*, 1385, 2407 (1993).
[102] H. Akita, I. Umezawa and H. Matsukura, *Chem. Pharm. Bull.*, **45**, 272 (1997).

[103] O. Miyata, T. Shinada, I. Ninomaya and T. Naito, *Tetrahedron Letters*, **32**, 3519 (1991).
[104] H. Inoue, K. Matsuki and T. Oh-ishi, *Chem. Pharm. Bull.*, **41**, 1521 (1993).
[105] K. Matsuki, M. Sobukawa, A. Kawai, H. Inoue and M. Takeda, *Chem. Pharm. Bull.*, **41**, 643 (1993).
[106] B. B. Lohray, B. Jayachandran, V. Bhushan, E. Nandanan and T. Ravindranathan, *J. Org. Chem.*, **60** 5983 (1995).
[107] O. Miyata, T. Shinada, I. Ninomiya and T. Naito, *Tetrahedron*, **53**, 2421 (1997).
[108] B. M. Adger, J. V. Barkley, S. Bergeron, M. W. Cappi, B. E. Flowerdew, M. P. Jackson, R. McCague, T. C. Nugent and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 3501 (1997).
[109] S. Yamada, K. Morimatsu, R. Yoshioka, Y. Ozaki and H. Seko, *Tetrahedron:Asymmetry*, **9**, 1713 (1998).
[110] S. Yamada, Y. Mori, K. Morimatsu, Y. Ishizu, Y. Ozaki, R. Yoshioka, T. Nakatani and H. Seko, *J. Org. Chem.*, **61**, 8586 (1996).
[111] S. Ohno, K. Izumi, K. Mizukoshi, K. Kato and M. Hori, *Chem. Pharm. Bull.*, **31**, 1780 (1983).
[112] S. Ohno, K. Mizukoshi, K. Izumi, K. Kato and M. Hori, *Chem. Pharm. Bull.*, **36**, 551 (1988).
[113] B. Letois, J. C. Lancelot, C. Saturnino, M. Robba and P. De Capraiis, *J. Heterocyclic Chem.*, **29**, 1769 (1992).
[114] J. Krapcho, US Patent 3,361,750 (1968); *Chem. Abstr.*, **69**, 36194 (1968).
[115] J. Krapcho, US Patent 3,748,321 (1973); *Chem. Abstr.*, **79**, 92303 (1973).
[116] J. Krapcho, US Patent 3,953,469 (1976); *Chem. Abstr.*, **85**, 21503 (1976).
[117] R. Di Santo, R. Costi, S. Massa and M. Artico, *Synth. Commun.*, **28**, 2517 (1998).
[118] M. Wilhelm and P. Schmidt, *Helv. Chim. Acta*, **53**, 1697 (1970).
[119] B. S. Pedersen, S. Scheibye, H. H. Nilsson and S.-O. Lawesson, *Bull. Soc. Chim. Belges*, **87**, 223 (1978).
[120] V. Ambrogi, G. Grandolini, C. Rossi and M. C. Tiralti, *Il Farmaco Ed. Sci.*, **42**, 575 (1987).
[121] A. Lévai, *Arch. Pharm. (Weinheim)*, **325**, 721 (1992).
[122] G. Bruno, A. Chimirri, R. Gitto, S. Grasso, F. Nicolo, R. Scopelliti and M. Zappala, *J. Chem. Soc., Perkin Trans. 1*, 2211 (1997).
[123] H. Bartsch and T. Erker, *Heterocycles*, **27**, 1461 (1988).
[124] H. Bartsch and T. Erker, *J. Heterocyclic Chem.*, **25**, 1151, 1399 (1988).
[125] H. Bartsch and T. Erker, *Sci. Pharm.*, **57**, 325 (1989).
[126] H. Bartsch and T. Erker, *Trends Heterocyclic Chem.*, **3**, 351 (1993).
[127] S. Pippich and H. Bartsch, *Heterocycles*, **43**, 1967 (1996).
[128] S. Pippich, H. Bartsch and W. Holzer, *Tetrahedron*, **53**, 8439 (1997).
[129] S. Pippich, H. Bartsch and T. Erker, *J. Heterocyclic Chem.*, **34**, 823 (1997).
[130] K.-H. Wüntsch, K.-H. Stahnke and A. Ehlers, *Chem. Ber.*, **103**, 2302 (1970).
[131] M. Miyazaki, T. Iwakuma and T. Tanaka, *Chem. Pharm. Bull.*, **26**, 2889 (1978).
[132] A. Lévai, *Acta Chim. Acad. Sci. Hung.*, **102**, 141 (1979).
[133] J. W. Skiles, R. Sorcek, S. Jacober, C. Miao, P. W. Mui, D. McNeil and A. S. Rosenthal, *Bioorg. Med. Chem. Letters*, **3**, 773 (1993).
[134] T. Patonay, W. Adam, J. Jekő, K. E. Kövér, A. Lévai, M. Németh and K. Peters, *Heterocycles*, **51**, 85 (1999).
[135] G. Kaupp, E. Gründken and D. Matthies, *Chem. Ber.*, **119**, 3109 (1986).
[136] G. Kaupp and D. Matthies, *Chem. Ber.*, **120**, 1741 (1987).
[137] H. Yanagisawa, K. Fujimoto, Y. Shimoji, T. Kanazaki, K. Mizutari, H. Nishino, H. Shiga and H. Koike, *Chem. Pharm. Bull.*, **40**, 2055 (1992).
[138] G. F. Katekar, *Aust. J. Chem.*, **25**, 1283 (1972).
[139] G. Trapani, A. Latrofa, M. Franco and G. Liso, *Il Farmaco*, **50**, 107 (1995).
[140] W. Ried and G. Sell, *Liebigs Ann. Chem.*, 1913 (1980).
[141] T. Blitzke, D. Sicker and H. Wilde, *J. Heterocyclic Chem.*, **34**, 453 (1997).
[142] L. K. Muskalo and U. P. Fedorova, *Ukr. Khim. Zh.*, **20**, 305 (1954).
[143] N. Ueyama, S. Wakabayashi and T. Tomiyama, *Chem. Pharm Bull.*, **45**, 1761 (1997).
[144] B. A. Zagorevskii and N. V. Dudykina, *Zh. Oshch. Khim.*, **33**, 322 (163).
[145] M. Karikomi, S. Yamori and T. Toda, *Heterocycles*, **35**, 619 (1993).
[146] J. Svetlik, V. Hanus and J. Bella, *Liebigs Ann. Chem.*, 91 (1989).
[147] W. Ried and G. Sell, *Chem. Ber.*, **113**, 2314 (1980).
[148] W. Ried and G. Sell, *Liebigs Ann. Chem.*, 1252 (1980).
[149] J. M. J. Tronchet and B. Gentile, *Helv. Chim. Acta*, **63**, 1779 (1980).
[150] Y. Ito, M. Wakimura, C. Ito and I. Maeba, *Heterocycles*, **34**, 2131 (1992).