Synthesis and Chemical Transformations of 1,4-, 4,1-, and 1,5-Benzoxazepines

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Dedicated to Professor Dr. Gábor Tóth on the occasion of his 60th birthday.

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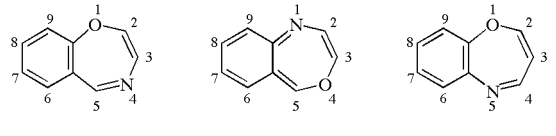
1. Introduction.

1,4-, 4,1-, and 1,5-Benzoxazepines are the benzocondensed derivatives of the 1,4-oxazepine. The skeletons of these three benzoxazepine types, together with the numbering of the atoms, are shown by Scheme 1. These parent compounds have not hitherto been described in the literature, but their derivatives belong to the most frequently studied benzoxazepines.

Scheme 1



1,4-Benzoxazepine 4,1-Benzoxazepine 1,5-Benzoxazepine

There are no general procedures for the synthesis of these structurally related compounds. However, in some cases both 1,4- and 1,5-benzoxazepine isomers are formed in a particular reaction which can then be separated by various techniques. For this reason, special synthetic procedures should be worked out for the preparation of each type of these three benzoxazepine isomers.

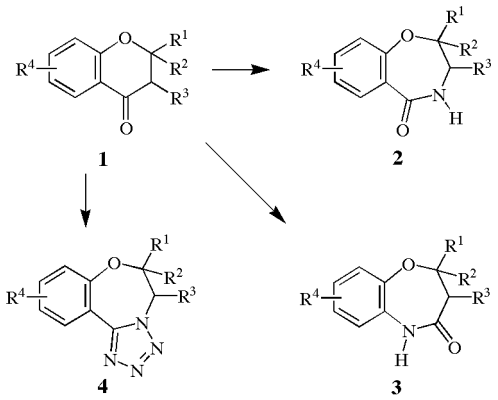
The major aim of this review article is to summarize the most important methods invented for the synthesis of these three groups of benzoxazepines. Some of their most important chemical transformations have also been included *via* adequate examples.

2. Synthesis of 1,4-Benzoxazepines.

This group is one of the most frequently investigated benzoxazepine type substances. Especially numerous 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-ones **2** have been synthesized mainly for biological and pharmaceutical purposes. One of the most common methods for the preparation of benzoxazepines **2** is the Schmidt reaction of the appropriate 4-chromanones **1** which has hitherto been investigated in several laboratories [1-12]. 4-Chromanones **1** are allowed to react with *in situ* liberated hydrazoic acid in an acidic medium to obtain 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-ones **2** (Scheme 2). In some cases, 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-ones **3** and/or tetrazole derivatives **4** have also been detected or isolated as minor products of the Schmidt reaction (Scheme 2) [5-7,10,12].

Mechanism of the Schmidt reaction of 4-chromanones **1** has been discussed [9,11,13]. According to the explanation

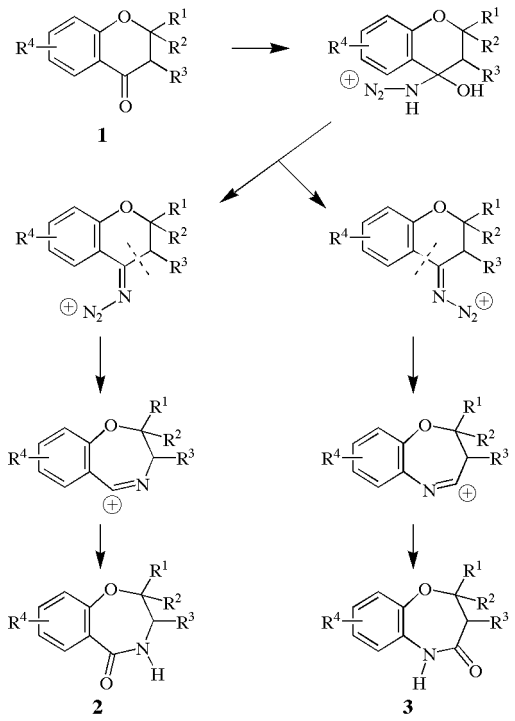
Scheme 2



$R^1 = R^2$: Me; R^3: H
R^1: Ar; $R^2 = R^3$: H
$R^1 = R^2$: H; R^3: Ar
R^4: Me, alkoxy, RSO_2O

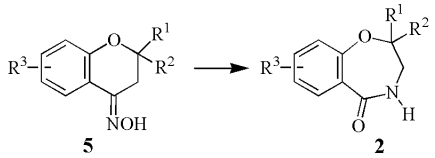
of Smith and Antoniades [13] a decisive factor is the stereochemistry of the iminodiazonium ion since the migration occurs *anti* to the diazonium nitrogens. It has been observed in the case of flavanones [9] and 2,2-dimethyl-4-chromanones [11] that the product is a 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one **2** if a hydrogen atom is present in the *peri*-position of the starting 4-chromanone **1** (Scheme 3).

Scheme 3



Another simple and convenient procedure for the preparation of 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-ones **2** by the ring enlargement of 4-chromanones **1** is the Beckmann rearrangement of their oximes **5** [14-16]. In case the oximes **5** of 4-chromanones and 2,2-dimethyl-4-chromanones (*cf.* **1** in Scheme 2) are allowed to react with polyphosphoric acid 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-ones **2** are formed if a hydrogen atom is attached to the *peri*-position of the starting 4-chromanone oximes **5** (Scheme 4) [14,15]. Therefore, it can be concluded that the Schmidt reaction of the 4-chromanones and the Beckmann rearrangement of their oximes lead to the formation of the same benzoxazepine isomers.

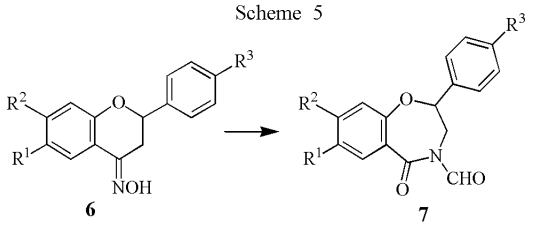
Scheme 4



$R^1 = R^2$: H; R^3: H, Me, Et, OMe, OEt, OPr
$R^1 = R^2$: Me; R^3: alkyl, alkoxy, RSO2O

An interesting chemical conversion is the Beckmann rearrangement of flavanone oximes **6** with a mixture of dimethylformamide and phosphorus oxychloride to afford 2-aryl-2,3-dihydro-4-formyl-1,4-benzoxazepin-5(4*H*)-ones **7** (Scheme 5) [16]. This is the sole example for the synthesis of *N*-formylbenzoxazepines by a ring enlargement reaction.

Scheme 5

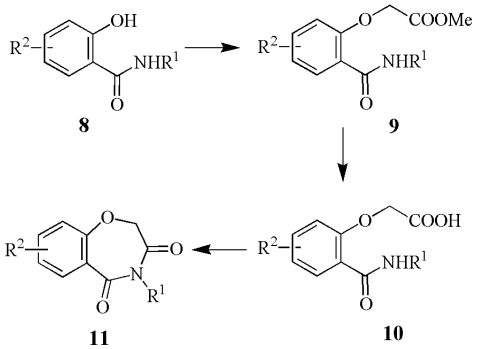


R^1: H, Me, Cl; R^2: H, Me; R^3: H, Me

Structure elucidation of these 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-ones have been performed mainly by various nmr spectroscopic measurements and by mass spectroscopy [17-20]. Conformation of the seven-membered ring has been determined in the case of their 2-substituted and 2,2-disubstituted derivatives by temperature-dependent nmr spectroscopy [17,19]. ^{1}H and ^{13}C nmr measurements unequivocally proved that the seven-membered ring of such benzoxazepines may adopt two boat conformers which rapidly interchange.

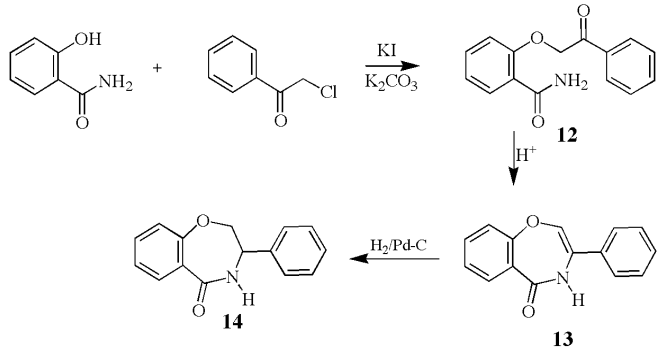
Recently, related group of such 1,4-benzoxazepines has been published in the literature by Kwiecien [21-23]. 2-Alkyl-2,3,4,5-tetrahydro-1,4-benzoxazepin-3,5-diones **11** have been synthesized starting from salicylamide derivatives **8**. The hydroxy group of compounds **8** was first alkylated with methyl bromoacetate to obtain esters **9** which were then saponified to yield carboxylic acids **10**. Cyclodehydratation of compounds **10** with acetic anhydride afforded 2-alkyl-2,3,4,5-tetrahydro-1,4-benzoxazepin-3,5-diones **11** (Scheme 6). Some of these 1,4-benzoxazepines showed moderate fungicide activity against *Botrytis cinerea* [22].

Scheme 6



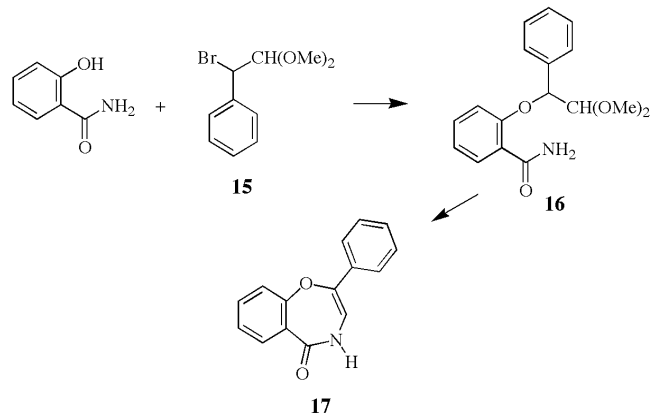
1,4-Benzoxazepin-5(4*H*)-ones have been synthesized starting from salicylamide. For the utilization of this procedure, the first example is the preparation of the 3-phenyl-1,4-benzoxazepin-5(4*H*)-one (**13**) by the acid catalyzed ring closure of the 2-phenacyloxybenzamide (**12**). Compound **13** gave then 2,3-dihydro-3-phenyl-1,4-benzoxazepin-5(4*H*)-one (**14**) on hydrogenation (Scheme 7) [24].

Scheme 7



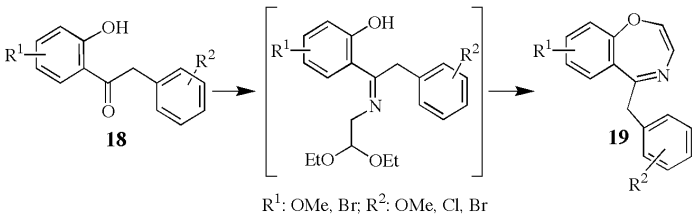
Kaye *et al*., [25,26] synthesized 2-phenyl-1,4-benzoxazepin-5(4*H*)-one *via* a stepwise cyclization of a bromoacetal and salicylamide intermediates. Reaction of the salicyclamide and bromoacetal **15** yielded *o*-(2,2-dimethoxy-1-phenylethyl)salicylamide (**16**) which then afforded compound **17** on an acid-catalyzed ring closure (Scheme 8) [25,26].

Scheme 8



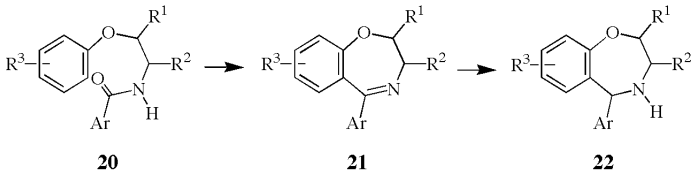
5-Benzyl-1,4-benzoxazepines **19** have been synthesized by the Pomeranz-Fritsch reaction by using 2-hydroxydeoxybenzoins **18** as starting materials. The 2-hydroxydeoxybenzoins **18** were allowed to react with aminoacetaldehyde diethyl acetal to obtain the appropriate Schiff bases which gave then 5-benzyl-1,4-benzoxazepines **19** on cyclization with polyphosphoric acid at 65-70° (Scheme 9) [27].

Scheme 9



Bischler-Napieralski cyclization of benzamides **20** with phosphorus oxychloride provided 5-aryl-2,3-dihydro-1,4-benzoxazepines **21**. Compounds **21** have been hydrogenated with the help of Adams platinum catalyst to obtain 5-aryl-2,3,4,5-tetrahydro-1,4-benzoxazepines **22** (Scheme 10) [28,29].

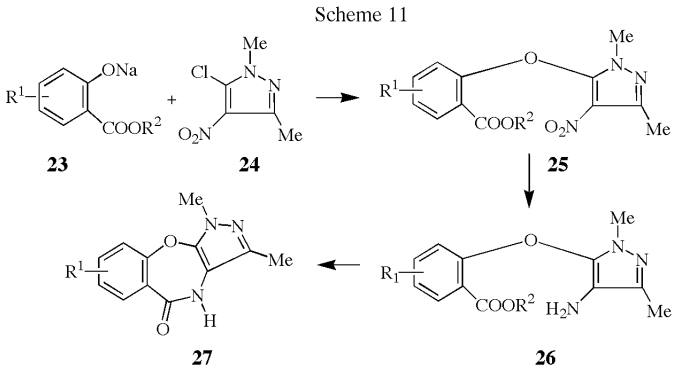
Scheme 10



Various groups of tricyclic benzoxazepines have also been published in the literature. Some of these substances possess bioactivities and, therefore, are useful compounds in drug research. Herein we show several examples for the synthesis of such tricyclic benzoxazepines.

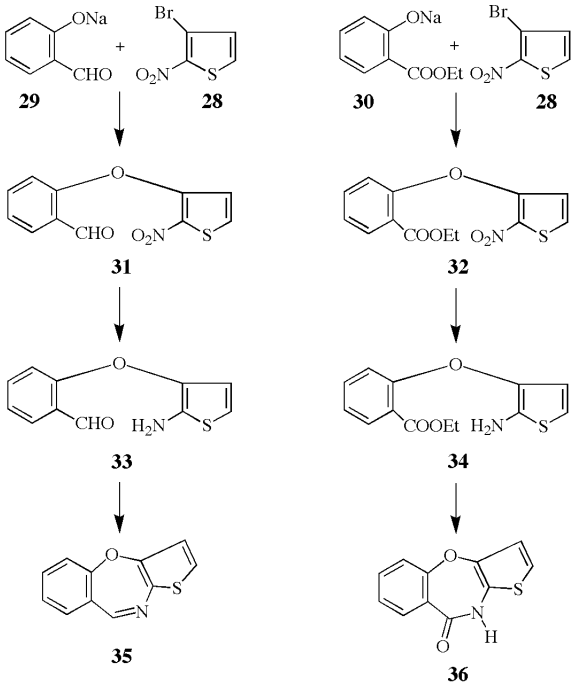
4,5-Dihydro-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*][1,4]benzoxazepines **27** have been prepared *via* a multistep procedure [30]. 2-Hydroxybenzoic acid derivatives **23** were allowed to react with 5-chloro-1,3-dimethyl-4-nitropyrazole (**24**) to obtain the nitrocarboxylic acid intermediates **25**. Compounds **25** have been hydrogenated to afford aminocarboxylic acids **26** which gave the appropriate tricyclic benzoxazepines **27** on ring closure (Scheme 11) [30].

Scheme 11



Thieno[2,3-*b*][1,4]benzoxazepines have been synthesized starting from the reaction of 3-bromo-2-nitrothiophene **28** with sodium salt of salicylaldehyde **29** or sodium ethyl salicylate **30** to obtain the 3-aroyloxy-2-nitrothiophenes **31** and **32** which yielded the appropriate amino derivatives **33** and **34** on hydrogenation as key intermediates for the ring closure reaction. Cyclization of compounds **33** and **34** provided the target thieno-[3,2-*b*][1,4]benzoxazepines **35** and **36** in moderate yields (Scheme 12) [31].

Scheme 12

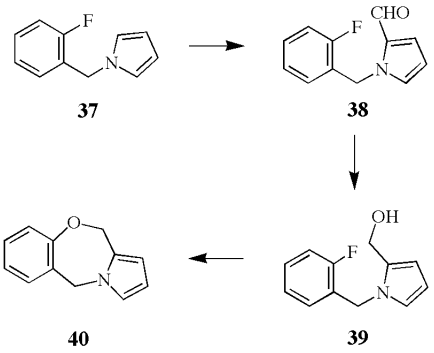


Pyrrolo[2,1-*c*][1,4]benzoxazepines have been synthesized *via* a multistep procedure (Scheme 13) [32]. Formylation of *N*-(2-fluorobenzyl)pyrrole (**37**) by Vilsmaier formylation with dimethylformamide and phosphorus oxychloride gave the 2-carboxaldehyde **38**. Aldehyde **38** provided the appropriate alcohol **39** on reduction with sodium borohydride. Compound **39** was then cyclized to obtain 5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzoxazepine (**40**) by using sodium hydride in a mixture of anhydrous benzene and dimethylformamide as solvent.

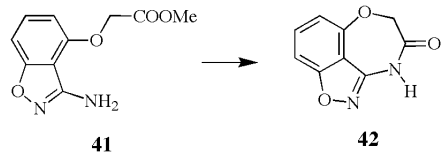
Isoxazolo[3,4,5-*e*,*f*][1,4]benzoxazepin-3(4*H*)-one **42** has been synthesized by the cyclization of 3-amino-4-[(methoxycarbonyl)methoxy]-1,2-benzisoxazole (**41**) with the help of sodium hydride in an anhydrous dimethylformamide solution (Scheme 14)[33].

Thieno[4,3,2-*e*,*f*][1,4]benzoxazepine, as a novel ring system, has been prepared *via* a multistep procedure starting from 3-amino-4-fluorobenzo[*b*]thiophene (**43**). Compound **43** was allowed to react with 4-chloropyridine

Scheme 13

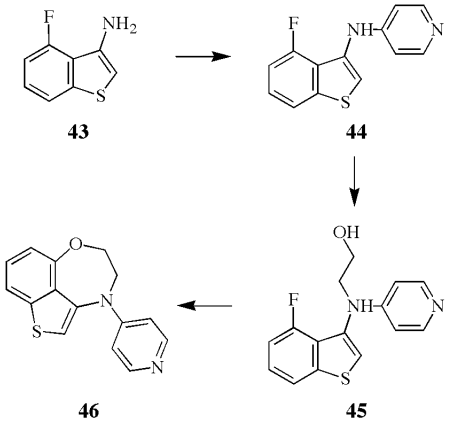


Scheme 14



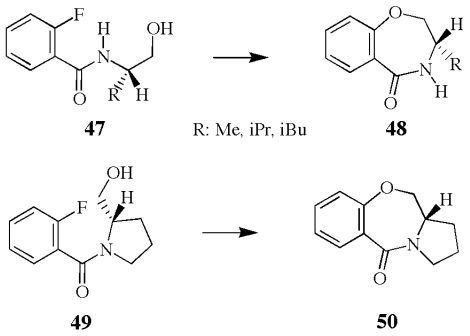
to obtain the *N*-arylated derivative **44**. *N*-β-hydroxyethyl side chain was then introduced to yield the intermediate **45** for ring closure. Cyclization of substance **45** afforded 4,5-dihydro-3-(4-pyridinyl)thieno[4,3,2-*e*,*f*][1,4]benzoxazepine (**46**) (Scheme 15) [34].

Scheme 15



Synthesis of optically active 1,4-benzoxazepines has also been described in the literature [35-37]. 3-Substituted derivatives **48** of the 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-one have been prepared by the cyclization of 2-fluorobenzamides **47** in anhydrous dimethylformamide in the presence of sodium hydride (Scheme 16) [35]. This procedure has been utilized for the synthesis of related tricyclic 1,4-benzoxazepines as well. Ring closure of compound **49** afforded the (3a*S*)-2,3,3a,4-tetrahydro-1*H*,10*H*-pyrrolo[2,1-*c*][1,4]benzoxazepin-10-one (**50**) (Scheme 16) [36].

Scheme 16

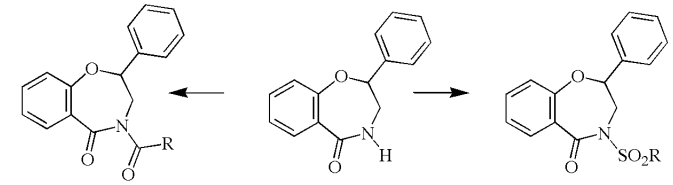


3. Chemical Transformations of 1,4-Benzoxazepines.

3.1 *N*-Acylation and *N*-Alkylation of 1,4-Benzoxazepin-5(4*H*)-ones.

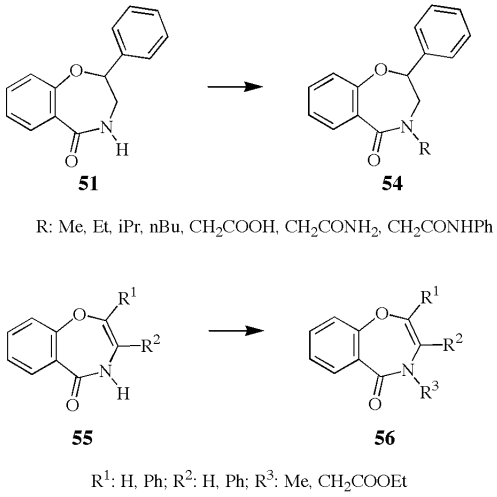
1,4-Benzoxazepines are considered to be useful compounds in drug research. Such a utilization usually requires the introduction of various side chains into the starting 1,4-benzoxazepine molecule. Reactivity of the nitrogen heteroatom can be exploited for this purpose. 2,3-Dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one (**51**) has been *N*-acylated either with a carboxylic acid chloride or anhydride to obtain *N*-acylated derivatives **52** (Scheme 17) [9,38]. In case mesyl chloride or benzenesulfonyl chloride were used as acylating agents together with anhydrous pyridine, *N*-substituted compounds **53** were obtained (Scheme 17) [38].

Scheme 17



N-Alkylation of the 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-one (**51**) has been performed by using various alkyl halides in anhydrous dimethylformamide in the presence of sodium hydride to afford 4-alkyl-2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-ones **54** (Scheme 18) [9,19,38]. 1,4-Benzoxazepin-5(4*H*)-ones **55** have also been *N*-alkylated by alkyl halides to yield *N*-alkylated derivatives **56** (Scheme 18) [26].

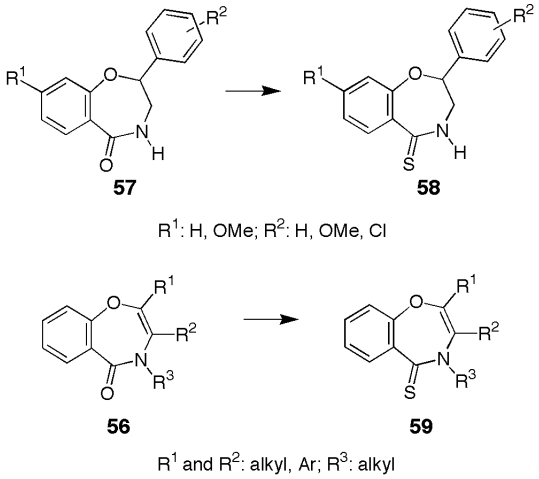
Scheme 18



3.2. Conversion of the Amides into Thioamides.

1,4-Benzoxazepin-5(4*H*)-ones have been converted into the appropriate 1,4-benzoxazepin-5(4*H*)-thiones with the help of different reagents. As a first example of this reaction, 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-ones **57** were allowed to react with phosphorus pentasulfide to obtain 2,3-dihydro-2-phenyl-1,4-benzoxazepin-5(4*H*)-thiones **58** (Scheme 19) [9]. Phosphorus pentasulfide has also been used for the conversion of 1,4-benzoxazepin-5(4*H*)-ones **56** into their thiones **59** (Scheme 19) [26].

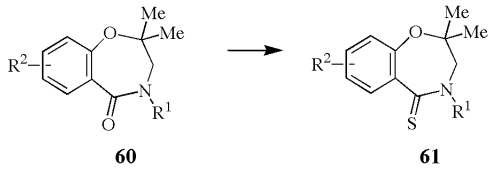
Scheme 19



For the conversion of such cyclic amides into thioamides there is a more convenient reagent *viz*. the Lawesson's Reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] [39]. Variously substituted 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-ones **60**

have been converted into the appropriate thiones **61** by using this efficient reagent (Scheme 20) [11,19,38].

Scheme 20



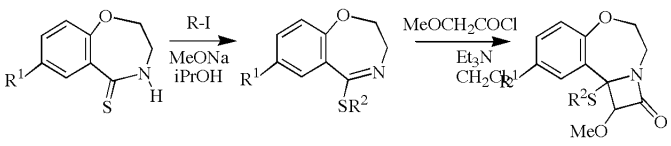
60 **61**

R^1: H, Me; R^2: H, Me, alkoxy, RSO_2O

3.3. Preparation of β-Lactam Derivatives Starting from Thioamides

Sulfur atom of the 2,3-dihydro-1,4-benzoxazepin-5(4*H*)-thiones **62** can be alkylated to yield alkyl thioimidates **63** (Scheme 21) [40]. Compounds **63** were then reacted with *in situ* generated ketenes to afford β-lactam derivatives **64** of 1,4-benzoxazepines (Scheme 21) [40].

Scheme 21



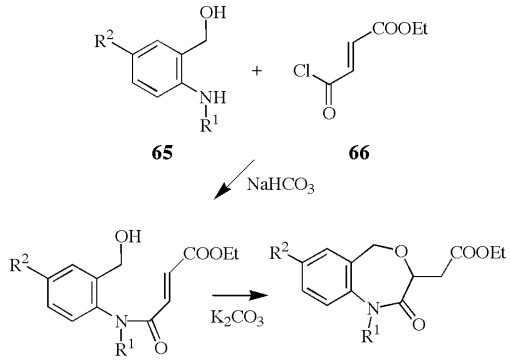
62 **63** **64**

R^1: H, Cl; R^2: Me, Et, iPr

4. Synthesis of 4,1-Benzoxazepines.

Synthesis of 4,1-benzoxazepines has hitherto received less attention and their few derivatives have been published in the literature. 1,2,3,5-Tetrahydro-2-oxo-4,1-benzoxazepines bearing a carboxylic acid side chain have been synthesized starting from aminoalcohols **65** in a two-steps procedure. Acylation of 2-aminobenzyl alcohols **65** with fumaric acid chloride monoethyl ester **66** yielded amides **67** ring closure of which afforded the desired 1,2,3,5-tetrahydro-2-oxo-4,1-benzoxazepines **68** (Scheme 22) [41].

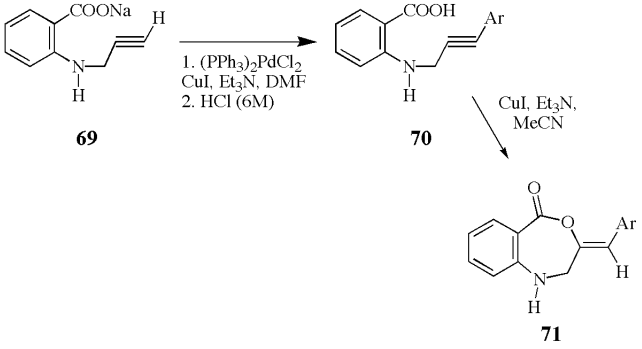
Scheme 22



65 **66**

Recently, Chaudhuri and Kundu [42] published an efficient procedure for the synthesis of (*Z*)-3-arylidene-1,2,3,5-tetrahydro-4,1-benzoxazepin-5-ones **71**. Sodium 2-(prop-2'-ynylamino)benzoate (**69**) was allowed to react with aryl iodides in the presence of bis(triphenylphosphine)palladium(II) chloride, cuprous iodide and triethylamine in a mixture of acetonitrile and dimethylformamide to yield carboxylic acids **70** which afforded (*Z*)-3-arylidene-1,2,3,5-tetrahydro-4,1-benzoxazepin-5-ones **71** (Scheme 23) [42].

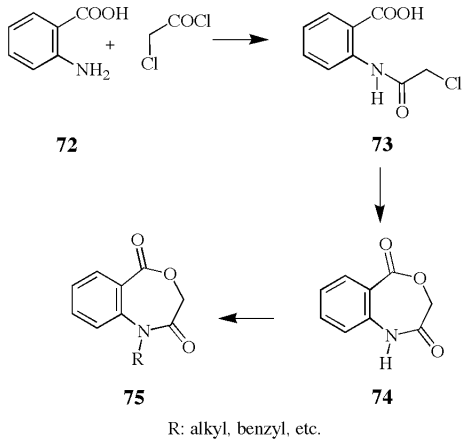
Scheme 23



69 **70** **71**

4,1-Benzoxazepin-2,5-diones **75** have been synthesized starting from anthranilic acid (**72**). Compound **72** was first *N*-acylated with chloroacetyl chloride to afford *N*-chloroacetylanthranilic acid (**73**) which was cyclized to obtain 4,1-benzoxazepin-2,5-dione **74**. Substance **74** was *N*-alkylated with alkyl halides in anhydrous dimethylformamide in the presence of sodium hydride to yield *N*-alkyl-4,1-benzoxazepin-2,5-diones **75** (Scheme 24) [43,44].

Scheme 24

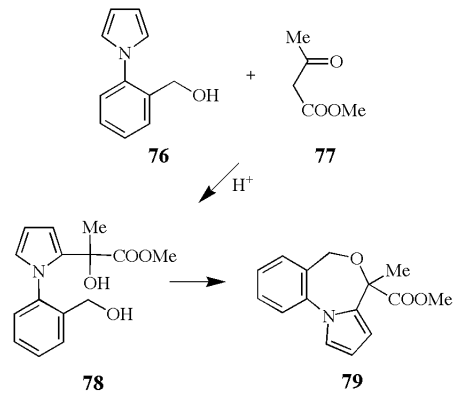


72 **73** **74** **75**

R: alkyl, benzyl, etc.

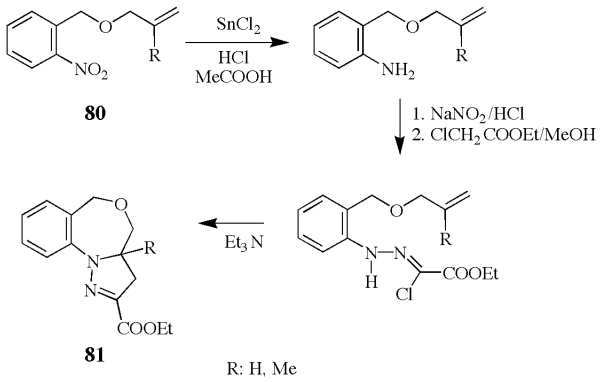
4,1-Benzoxazepines condensed with a five- or six-membered heterocyclic ring have also been synthesized [45-48]. 4*H*,6*H*-Pyrrolo[1,2-*a*][4,1]benzoxazepine (**79**) has been synthesized starting with the reaction of *N*-[(2-hydroxymethyl)phenyl]pyrrole (**76**) with methyl pyruvate (**77**) to yield a carboxylic acid derivative **78**. Compound **78** gave the target 4,1-benzoxazepines **79** on ring closure (Scheme 25) [45].

Scheme 25



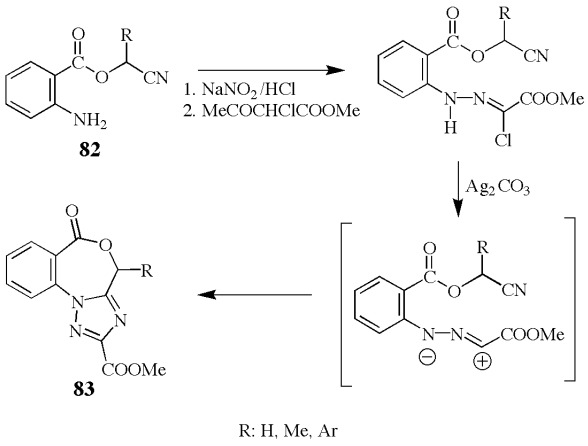
2-Ethoxycarbonyl-3,3a-dihydro-4*H*,6*H*-pyrazolo-[1,5-*a*][4,1]benzoxazepines **81** have been prepared starting from 3-(2-nitrobenzyloxy)propenes **80** *via* reaction steps shown by Scheme 26 [46].

Scheme 26



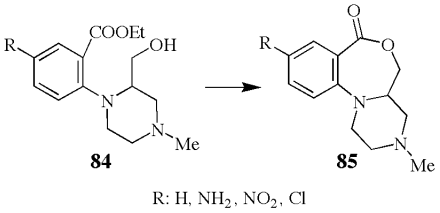
Diazotation and further chemical transformations of 2-aminobenzoic acid esters **82** outlined in Scheme 27, *viz.* coupling with methyl 2-chloroacetoacetate followed by the elimination of hydrochloric acid on treatment with silver carbonate, lead to the formation of [1,2,4]triazolo[1,5-*a*][4,1]benzoxazepines **83** as a third group of the hitherto known tricyclic 4,1-benzoxazepines (Scheme 27)[47].

Scheme 27



Pyrazino[1,2-*a*][4,1]benzoxazepines **85** have been prepared by the ring closure of 2-aminobenzoic acid derivatives **84** in a hot mixture of toluene and triethylamine (Scheme 28) [48].

Scheme 28

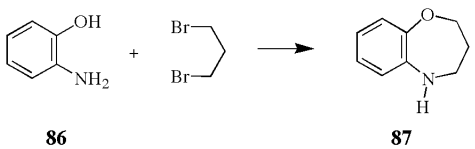


5. Synthesis of 1,5-Benzoxazepines.

1,5-Benzoxazepines comprise the second largest group of benzoxazepines. For the synthesis of their tetrahydro derivatives various procedures have been worked out. Optically active 1,5-benzoxazepines have also been described in the literature.

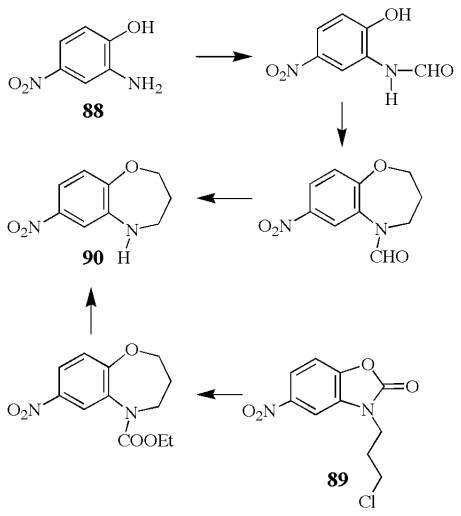
The simplest known derivatives of the 1,5-benzoxazepines are the 2,3,4,5-tetrahydro-1,5-benzoxazepines. The 2,3,4,5-tetrahydro-1,5-benzoxazepine (**87**) itself has been synthesized by the reaction of the 2-aminophenol (**86**) with 1,3-dibromopropane in anhydrous dimethylformamide in the presence of sodium hydride (Scheme 29) [49].

Scheme 29



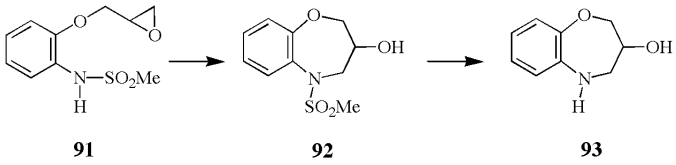
The 7-nitro-2,3,4,5-tetrahydro-1,5-benzoxazepine (**90**) has been synthesized by using two different multistep procedures outlined in Scheme 30. Starting material of one of these two procedures is the 2-amino-4-nitrophenol (**88**) [50]. While the other method is based on a ring enlargement reaction of the 3-(3-chloropropyl)-5-nitro-3*H*-benzoxazol-2-one (**89**) (Scheme 30) [51].

Scheme 30



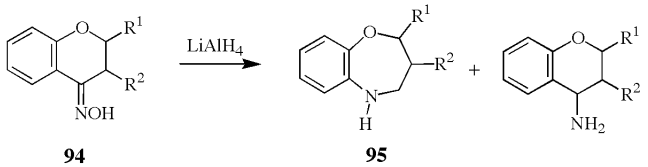
3-Hydroxy-5-(methylsulphonyl)-2,3,4,5-tetrahydro-1,5-benzoxazepine (**92**) has been prepared by the cyclization of the *N*-mesylated 2-aminophenol derivative **91** (Scheme 31) [52]. Compound **92** was then demesylated to afford the 3-hydroxy-2,3,4,5-tetrahydro-1,5-benzoxazepine (**93**).

Scheme 31



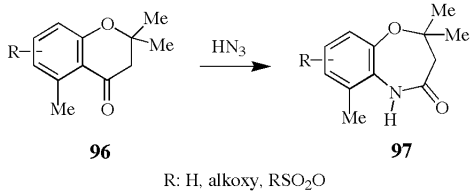
Among the products of the lithium aluminum hydride reduction of 4-chromanone oximes **94** there are 2,3,4,5-tetrahydro-1,5-benzoxazepines **95** as well (Scheme 32) [53-56]. However, this procedure cannot be considered as a practical synthesis of such benzoxazepines since the major product of this reaction is a 4-aminochroman type compound.

Scheme 32



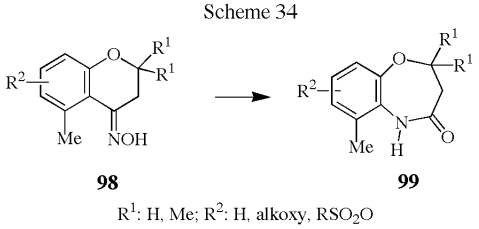
Schmidt reaction of 2,2,5-trimethyl-4-chromanones **96** affords 2,3-dihydro-2,2,6-trimethyl-1,5-benzoxazepin-4(5*H*)-ones **97** (Scheme 33) [11]. Formation of such 1,5-benzoxazepine isomer may be a consequence of the presence of a methyl group at the *peri*-position of the 4-chromanone favouring an aryl migration. Such an aryl migration is the prerequisite for a ring enlargement providing 1,5-isomers.

Scheme 33



Beckmann rearrangement of 5-methyl-4-chromanone oximes **98** yields 2,3-dihydro-6-methyl-1,5-benzoxazepin-4(5*H*)-ones **99** (Scheme 34) [14,15] similarly to the Schmidt reaction of the appropriate 4-chromanones (*vide supra*). Therefore, both the Schmidt reaction of the 5-methyl-4-chromanones and the Beckmann rearrangement of their oximes afford the same benzoxazepine isomers, *viz.* 1,5-benzoxazepines.

Scheme 34



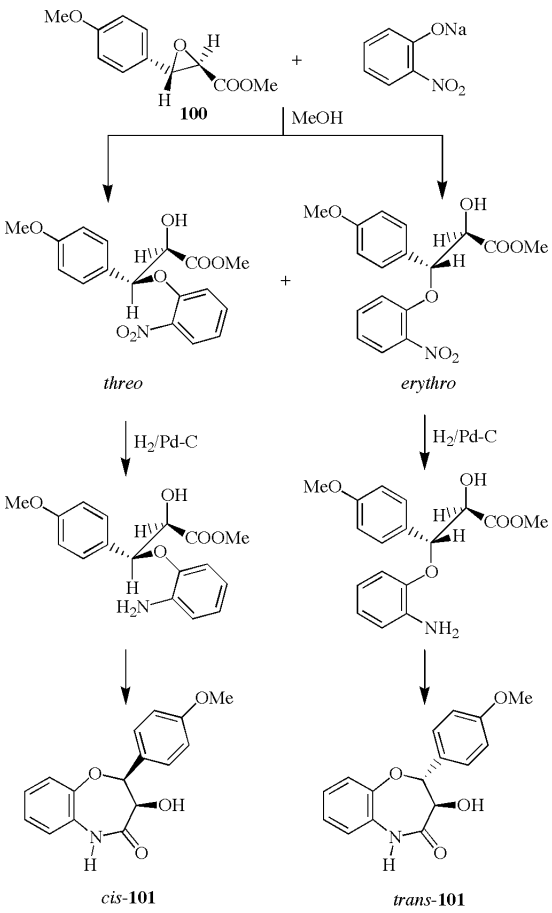
Both *trans*- and *cis*-isomers of the 2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzoxazepin-4(5*H*)-one **101** have been prepared starting from *trans*-3-(4-methoxyphenyl)glycidate **100** according to a multistep synthetic protocol (Scheme 35) [57]. 1,5-Benzoxazepine isomers obtained in this way have also been converted into their 5-diaminoalkyl derivatives for drug research purposes.

2-Aminophenols **86** were allowed to react with dithiomalonic acid *S*,*S*-diphenyl ester (**102**) to yield 1,5-benzoxazepin-2,4(3*H*,5*H*)-diones **103** (Scheme 36) [58,59].

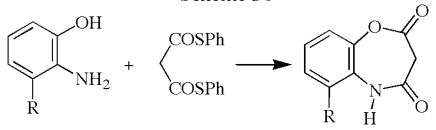
Synthesis of tricyclic 1,5-benzoxazepines with five- or six-membered heterocycle fused to the seven-membered ring of the benzoxazepines have also been described in the literature [60]. Such polycyclic benzoxazepines seem to be useful compounds in drug research.

Pyrrolo[2,1-*d*][1,5]benzoxazepine (**106**) has been synthesized starting with the reaction of the 2-(1-pyrrolyl)phenol

Scheme 35



Scheme 36



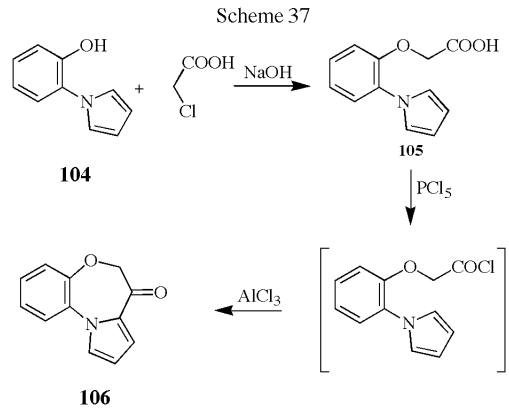
R: H, Me

(**104**) and chloroacetic acid to afford carboxylic acid **105** which was then cyclized to yield the target tricyclic benzoxazepine **106** (Scheme 37) [61].

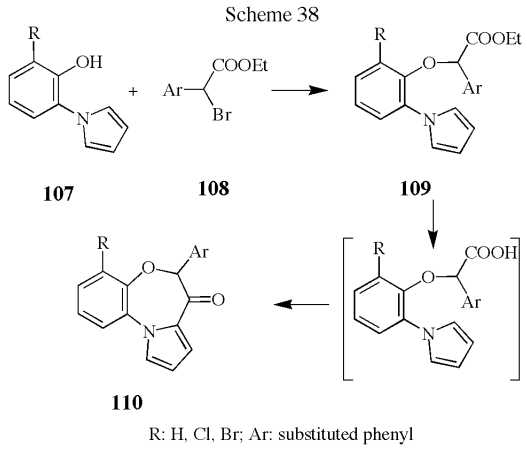
9-Arylpyrrolo[2,1-*d*][1,5]benzoxazepin-7(6*H*)-ones **110** have been synthesized by Nacci *et al.*, [62] according to a multistep protocol shown by Scheme 38. This synthesis also starts with the *O*-alkylation of 2-(1-pyrrolyl)phenols **107** with carboxylic acid esters **108** to obtain esters **109** which give then the target benzoxazepines **110** on saponification and ring closure (Scheme 38) [62].

Another group of the tricyclic 1,5-benzoxazepines with a fused five-membered heterocycle comprises the 9*H*,10-oxothieno[3,2-*b*][1,5]benzoxazepines **115**. Synthesis of such a ring system starts with the reaction of a

Scheme 37



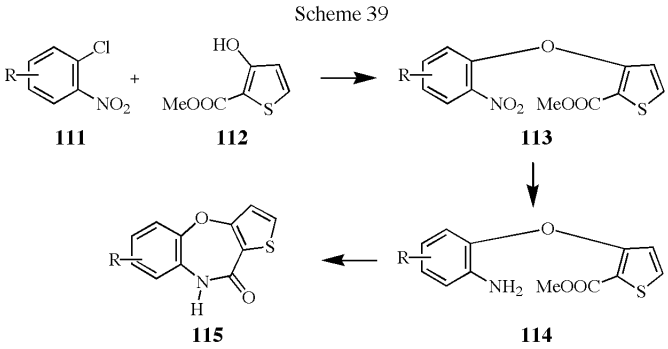
Scheme 38



R: H, Cl, Br; Ar: substituted phenyl

2-chloro(nitrobenzene) **111** with methyl 3-hydroxythiophene-2-carboxylate **112** to obtain arylthienyl ethers **113**. These ethers are then reduced to obtain the appropriate amino compounds **114** ring closure of which yields benzoxazepines **115** (Scheme 39) [63].

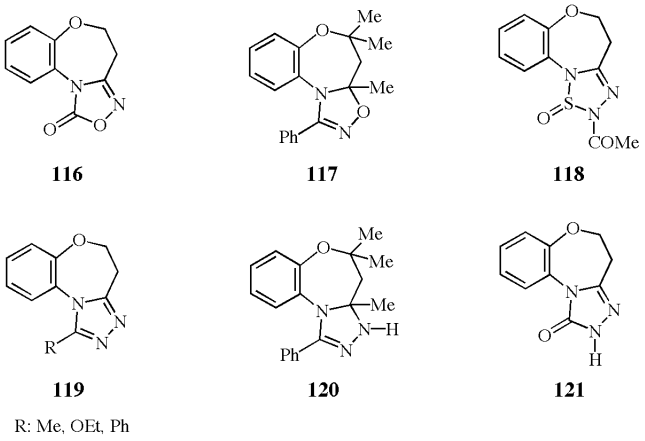
Scheme 39



Tricyclic 1,5-benzoxazepines **116-121**, shown by Scheme 40, fused with five-membered heterocycle possessing more than one heteroatom have also been prepared by particular procedures (Scheme 40) [64,65]. Reaction of 2,3-dihydro-3-methylthio-1,5-benzoxazepine with carbonyldiimidazole

afforded compound **116**. This starting material was then converted into compounds **118**, **119** and **121** by using acylhydrazides as reagents in glacial acetic acid as solvent [65]. While substances **117** and **120** were obtained by the reaction of 2,3-dihydro-2,2,4-trimethyl-1,5-benzoxazepine with *in situ* generated benzonitrile oxide [64].

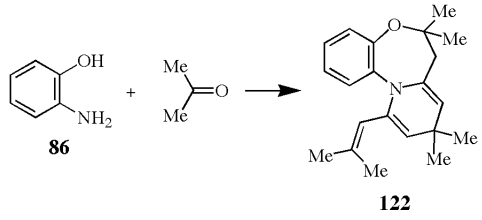
Scheme 40



R: Me, OEt, Ph

Few 1,5-benzoxazepines condensed with a six-membered heterocyclic ring have also been published in the literature [66-68]. 7,9-Dihydro-6,6,9,9-tetramethyl-11-(2-methylpropenyl)-6*H*-pyrido[2,1-*d*][1,5]benzoxazepine (**122**) have been synthesized by the reaction of 2-aminophenol (**86**) and a large excess of acetone, as solvent and reagent, in the presence of *p*-toluenesulfonic acid catalyst (Scheme 41) [66,67]. However, no mechanism of the reaction has been mentioned in the original papers describing the synthesis of compound **122**.

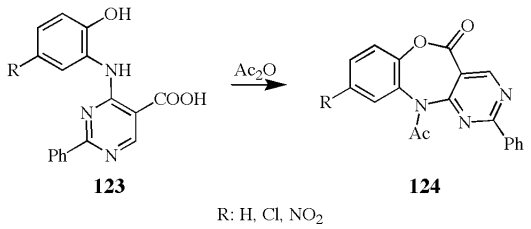
Scheme 41



2-Phenylpyrimido[5,4-*c*][1,5]benzoxazepin-5(1*H*)-ones **124** have been prepared by the ring closure of 4-(2-hydroxyamino)-2-phenyl-5-pyrimidenecarboxylic acids **123** with acetic anhydride (Scheme 42) [68].

Optically active 1,5-benzoxazepines have also been published in the literature. 3(*S*)-amino-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one has been synthesized starting by the reaction of 2-fluoro(nitrobenzene) (**125**) and *N*-protected-*L*-serine (**126**). The nitrocarboxylic acid **127** prepared in this way gave then aminocarboxylic acid **128** cyclization of

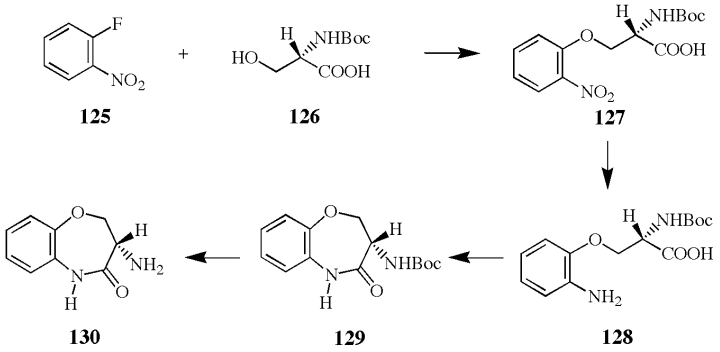
Scheme 42



R: H, Cl, NO_2

which afforded 1,5-benzoxazepine **129**. Deprotection of the amino group yielded the 3(*S*)-amino-2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one **130** (Scheme 43) [69-71].The origin of the 3*S* absolute configuration of this benzoxazepine is the *L*-serine as building block.

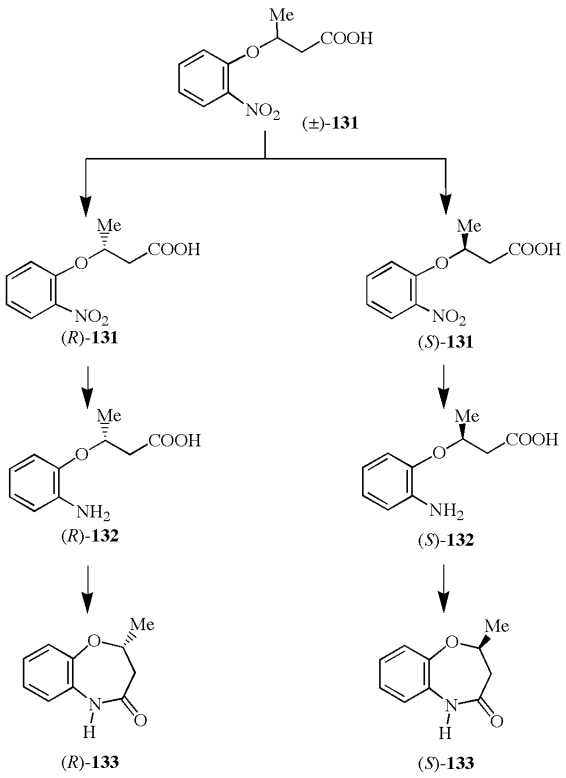
Scheme 43



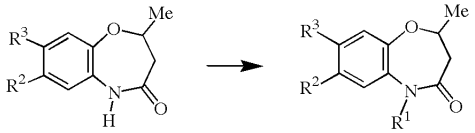
Other group of thoroughly investigated optically active 1,5-benzoxazepines comprises 2,3-dihydro-2-methyl-1,5-benzoxazepin-4(5*H*)-ones **133**. These optically active 1,5-benzoxazepines have been synthesized starting with an optical resolution of the 3-(2-nitrophenoxy)butyric acid **131** [72] *via* the fractional crystallization of its brucine salt [73] or by its enzyme-catalyzed kinetic resolution [74]. The optically active nitrocarboxylic acids **131** were then reduced to aminocarboxylic acids **132**, cyclization of which yielded the 2*R* and 2*S* enantiomers of the 2,3-dihydro-2-methyl-1,5-benzoxazepin-4(5*H*)-one **133** (Scheme 44) [73]. Numerous optically active derivatives **134** (Scheme 45) of both enantiomers of **133** have been prepared by various chemical transformations [73]. Conformational analysis of all these optically active 1,5-benzoxazepines has been performed by nmr spectroscopy [75]. Absolute configuration of their centre of chirality has been determined by circular dichroism spectroscopy [76,77].

As the newest group of optically active 1,5-benzoxazepines, 2,3-dihydro-3-hydroxy-1,5-benzoxazepin-4(5*H*)-ones **138** have been synthesized by the ring closure of carboxamide **137** obtained by the reaction of 2-aminophenols **135** with optically active oxirane carboxylic acid **136** (Scheme 46) [78].

Scheme 44

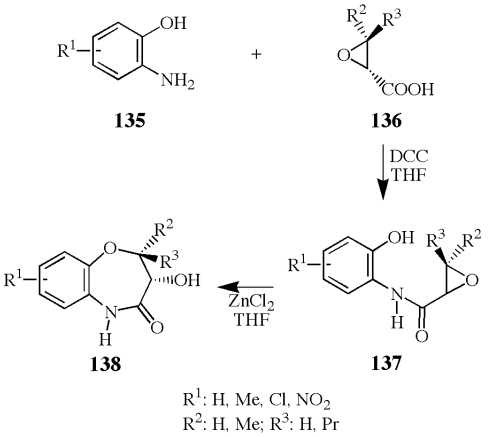


Scheme 45



R^1: H, Me, Ac
R^2: H, OH, OMe, Ac, OAc, COOH
R^3: H, Cl, Br, NO_2, NH_2, NHAc

Scheme 46



R^1: H, Me, Cl, NO_2
R^2: H, Me; R^3: H, Pr

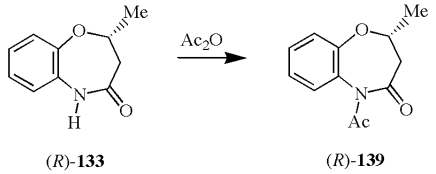
6. Chemical Transformations of 1,5-Benzoxazepines.

6.1. *N*-Acylation and *N*-Alkylation Reactions.

Since benzoxazepines are used in drug research, it is necessary to build appropriate side chains in their molecules. The nitrogen heteroatom is a convenient site to attach a side chain to the benzoxazepine skeleton which may take place by an acylation or an alkylation reaction.

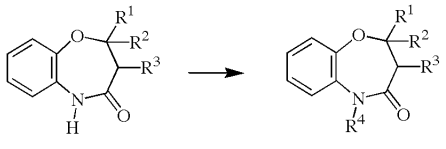
N-Acylation of the 1,5-benzoxazepines has hitherto received less attention. To our knowledge, the only example for such a chemical transformation is the preparation of the 5-acetyl-2,3-dihydro-2(*R*)-methyl-1,5-benzoxazepin-4(5*H*)-one (**139**) obtained by the reaction of the (*R*)-**133** with acetic anhydride in the presence of anhydrous pyridine (Scheme 47) [73].

Scheme 47



However, the *N*-alkylation of the 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-one type compounds is well documented in the literature [51,52,57,69-71,73,79]. The starting 1,5-benzoxazepine **140** is generally allowed to react with the apropriate alkyl halide in anhydrous dimethylformamide in the presence of sodium hydride to afford the *N*-alkylated derivatives **141** (Scheme 48). Some of these N-alkylated derivatives proved to be biologically active compounds, possessing *e.g* angiotensin converting enzyme inhibitory activity [69-71].

Scheme 48

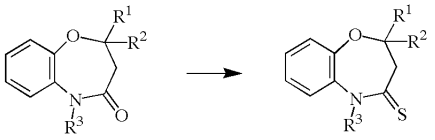


R^1: H, Me; R^2: H, Me; R^3: H, NH_2
R^4: alkyl, alkylamino, alkylcarboxy, *etc.*

6.2. Conversion of the Amides into Thioamides.

An interesting chemical transformation of the 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-ones **142** is their conversion into 2,3-dihydro-1,5-benzoxazepin-4(5*H*)-thiones **143** (Scheme 49). Compounds **142** are allowed to react with Lawesson's Reagent [39] to afford thiones **143** [11,19,59,73,80].

Scheme 49



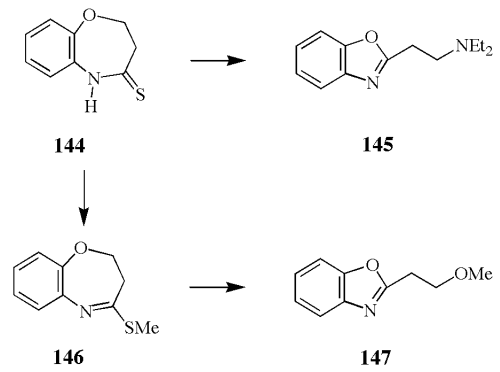
142 **143**

R^1: H, Me; R^2: H, Me; R^3: H, alkyl

6.3. Ring Contraction.

Ring contraction is an opportunity to convert the 1,5-benzoxazepines into other group of nitrogen- and oxygen-containing heterocyclic compounds with a smaller heterocycle. The 2,3-dihydro-1,5-benzoxazepin-4(5*H*)thione **144** can be considered as an activated benzoxazepine capable of ring contraction. If compound **144** is allowed to react with diethylamine 2-[2-(diethylamino)ethyl]benzoxazole (**145**) is obtained in high yield. Compound **144** can also be *S*-methylated to afford 2,3-dihydro-4-methylthio-1,5-benzoxazepine (**146**). This 1,5-benzoxazepine can be converted into 2-(2-methoxyethyl)benzoxazole (**147**) on treatment with sodium methoxide (Scheme 50) [80].

Scheme 50



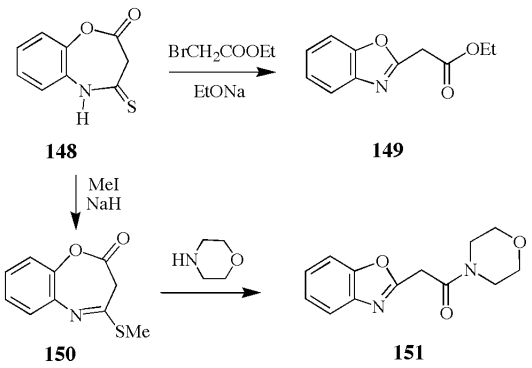
144 **145**

146 **147**

The 4,5-dihydro-4-thioxo-1,5-benzoxazepin-2(3*H*)-one (**148**) provides 2-[(ethoxycarnbonyl)methyl]benzoxazole (**149**) on treatment with ethyl bromoacetate and sodium ethoxide [59]. Compound **148** can also be converted in 4-(methylthio)-1,5-benzoxazepin-2(3*H*)-one (**150**) with iodomethane in the presence of sodium hydride which was then rearranged into benzoxazole **151** on treatment with morpholine (Scheme 51) [59].

In summary, in this review article most procedures worked out for the synthesis of 1,4-, 4,1-, and 1,5-benzoxazepines are compiled. Their most important chemical transformations are discussed as well. Literature data published till the end of 2000 have been included as references to help the readers to find the original publication concerning the synthesis and chemical transformations of a particular benzoxazepine.

Scheme 51



148 **149**

150 **151**

Acknowledgement.

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[*] The survey of the literature was covered until the end of 2000.

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