

Chemistry and biological activity of 1,3,4-benzotriazepines, part 3¹

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1. Introduction
2. Chemistry
 - 2.1. Syntheses modifying the parent system by substitution
 - 2.2. Syntheses of heterocyclic anellated 1,3,4-benzotriazepines
 - 2.3. Chemical behavior and structural investigations
3. Biological activity

1. Introduction

The discovery of the CNS activity of the 1,4-benzodiazepines directed increased attention to the isosteric 1,3,4-benzotriazepines. However, the representative compounds tested did not yield useful psychotropic drugs. However, these compounds showed remarkable profiles of biological activity and are of interest as potential leads for novel bioactive agents. This publication continues the overview (see [1, 2])² of the research activities in the 1,3,4-benzotriazepine series during the nineties, which has resulted in a variety of additional 2-amino- or 2-iminosubstituted and a-anellated as well as the novel c-anellated derivatives.

2. Chemistry

2.1. Syntheses modifying the parent system by substitution

2.1.1. 5-Aryl and 5-heteroaryl substituted 1,3,4-benzotriazepines

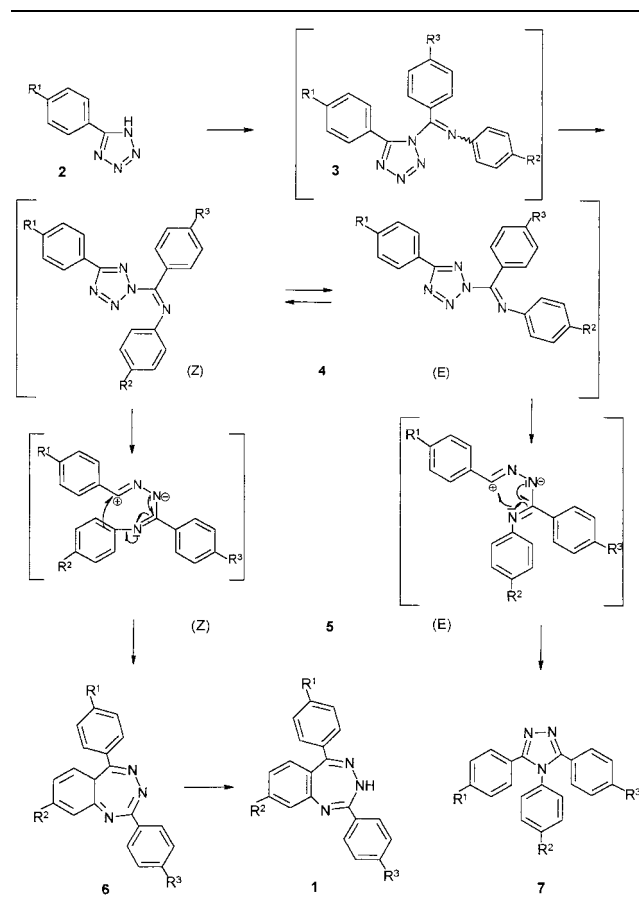
Koldobskii et al. [5–7] synthesized the 2,5-phenyl-3*H*-1,3,4-benzotriazepines **1a–j** (Table 1) by a reaction of the 5-aryltetrazoles **2** with *N*-arylbenzimidoyl chlorides (Scheme 1). The authors studied the influence of the reaction conditions and the effects of substitution at the aromatic ring on the formation of the reaction products.

Table 1: 2,5-Diphenyl-3*H*-1,3,4-benzotriazepines

Compd.	R ¹	R ²	R ³	Ref.
1a	H	H	H	[5–7]
1b	CH ₃	H	H	[5–7]
1c	Cl	H	H	[5–7]
1d	H	H	CH ₃	[6, 7]
1e	H	H	CH ₃ O	[6, 7]
1f	H	H	Br	[6, 7]
1g	H	CH ₃	H	[6, 7]
1h	H	Br	H	[5–7]
1i	H	H	NO ₂	[6]
1j	H	NO ₂	H	[6]

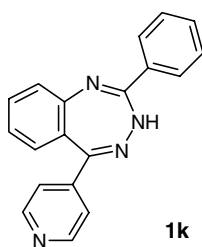
Thus, heating of the starting materials at 85–100 °C in the absence or presence of solvents (toluene, dioxane, pyridine, benzonitrile) for several hours provided the related 3,4,5-triaryl-1,2,4-triazoles **7**, regardless of polarity and basicity of the solvent. The authors explain the isolation of compound **7** by formation of the 1-imidoyltetrazoles **3** in the first step of the reaction cascade, which quickly rearranged to the analogous 2-imidoyltetrazoles **4** at higher temperatures. Both **3** and **4** were mixtures of the related (*Z*)- and the predominating (*E*)-isomers. Simultaneously, thermolysis of the two configuration isomers of **4** took place under nitrogen extrusion. The good yields of **7** (60–80%) were the result of different energy barriers between that of the *E* → *Z* isomerization and that of the thermolysis

Scheme 1



(smaller than in isomerization). Under the reaction conditions, the (*Z*)-isomers of **5** were formed in much lower concentrations than the related (*E*)-products, which cyclized via the imidoyl nitrogen to the final products **7** (Scheme 1). For this reason, only very small amounts of the 2,5-diaryl substituted 3*H*-1,3,4-benzotriazepines **1** were produced as byproducts.

When the 5-aryltetrazoles **2** reacted with the *N*-arylbenzimidoyl chlorides at room temperature within the two phase system dichloromethane (or chloroform) – aqueous sodium hydroxide solution in the presence of the phase transfer catalysts tetrabutylammonium bromide [6, 7] and 2,3-diphenyl-5-butyltetrazolium bromide [5], respectively, the solvent-free mixtures of the crude products **3** and **4** could be isolated. On the basis of the reaction of the 5-phenyltetrazole **2a** with *N*-phenylbenzimidoyl chloride, it was established by ¹³C NMR spectroscopy that the related compounds **3a/4a** ($R^1 - R^3 = H$), (*Z*)-**3a**/(*E*)-**3a**, and (*Z*)-**4a**/(*E*)-**4a** were formed ratios of 1.01, 1.50, and 0.94, respectively [6]. By heating the mixtures formed in toluene, dioxane, benzonitrile, and in the absence of the solvent at 85–95 °C, the 2,5-diaryl-3*H*-1,3,4-benzotriazepines **1** were obtained in good yields. The 5-(4-pyridyl) derivative **1k** [6] was synthesized in the same way.



Scheme 2

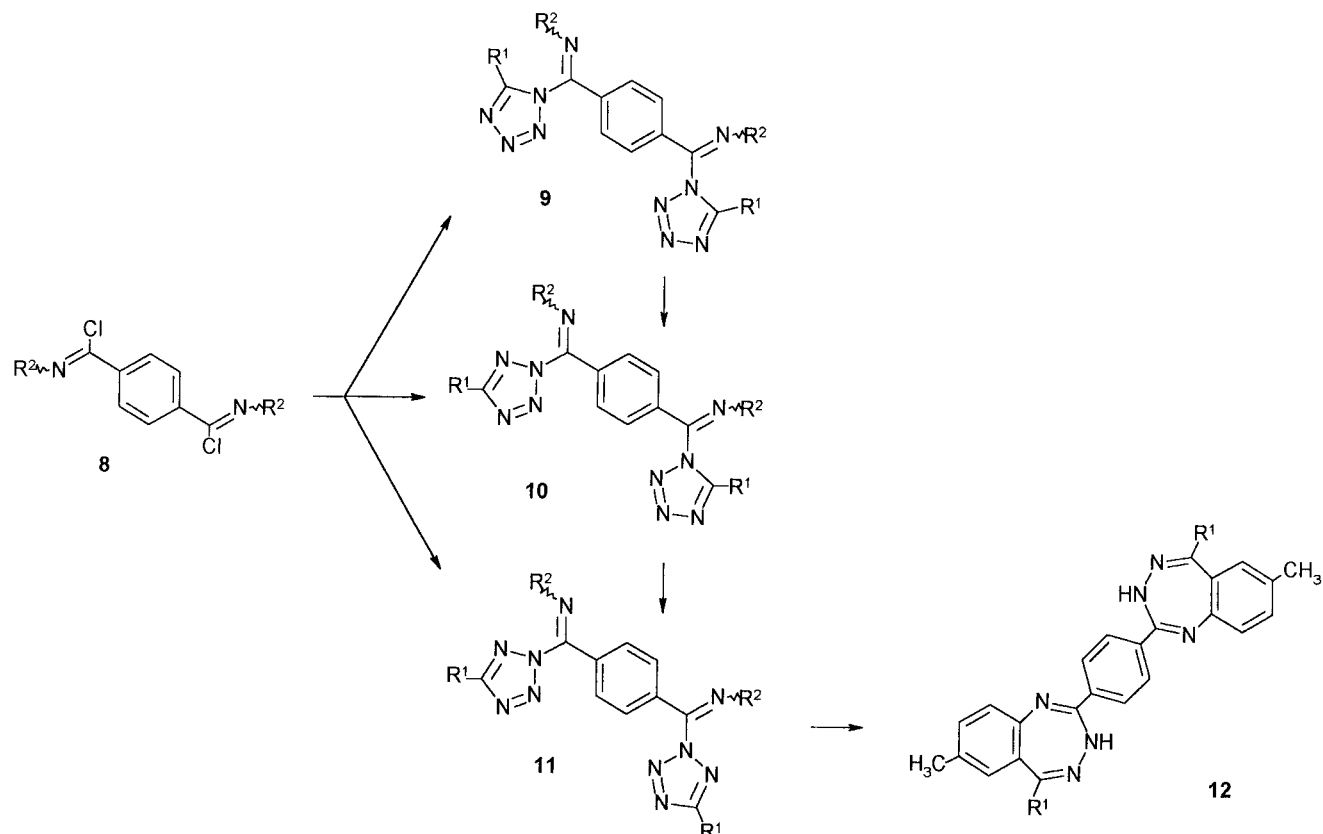
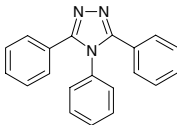
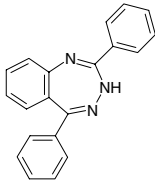
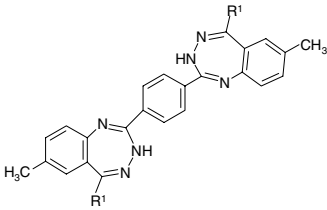


Table 2: Influence of the solvent on the formation of thermolysis products (yield in%) [7]

Solvent		
—	—	33
Toluene	—	65
Dioxane	—	63
Pyridine	21	31
Benzonitrile	—	71
Dimethylformamide	17	25

The course of reaction can be explained by the fact that the (*Z*)-forms predominate, to start with **3** (see before), after thermal isomerization with **4**, and after loss of nitrogen with **5**. The latter were transformed into the products **1** via the tautomers **6** by intramolecular cyclization involving the *N*-aryl ring. Using basic solvents, such as pyridine and dimethylformamide, an increased formation of the 1,2,4-triazoles **7** was noticed. This compound could be isolated from the product mixtures together with the related **1**. The influence of the solvent on the yields of 1,3,4-benzotriazepine and 1,2,4-triazole in the preparation of **1a** is shown in table 2. The substitution of the *N*-aryl ring of the starting *N*-arylbenzimidoyl chlorides partially controls the formation of the final reaction products. Substituents possessing strong electron withdrawing properties, such as in *N*-(4-nitrophenyl)benzimidoyl chloride, do not direct the reaction to the 7-nitro-3*H*-1,3,4-benzotriazepine, but to the related 4-(4-nitrophenyl)-1,2,4-triazole. Due to the reduced nucleophi-

Table 3: 2,2'-(1,4-Phenylen)bis(7-methyl-5-phenyl-3*H*-1,3,4-benzotriazepines) [8]

	
Compd.	R ¹
12a	C ₆ H ₅
12b	4-Cl–C ₆ H ₄
12c	4-CH ₃ O–C ₆ H ₄

licity of the aromatic ring, the cyclization now proceeds by attack of the imidoyl nitrogen atom which is more nucleophile compared with the ring. On the other hand, substituents with electron donor or only weak electron withdrawing properties do not substantially affect the course of the thermolysis [7].

Based on these investigations, Artamonova and Koldobskii allowed the 5-aryltetrazoles **2** to react with *N,N'*-bis(4-methylphenyl)-terephthalamidoyl dichloride **8** within the two phase system dichloromethane (or chloroform) – aqueous sodium hydroxide solution under the conditions cited above, which resulted in the formation of the thermic instable products **9–11** (R¹ = 4-CH₃O–C₆H₄, C₆H₅, 4-Cl–C₆H₄; R² = 4-CH₃–C₆H₄). After removing the solvent, the mixture of these products was thermolyzed as was done with **3**

and **4** [5–7]. This led to the yellow coloured derivatives **12a–c** of 2,2'-(1,4-phenylen)bis(7-methyl-5-phenyl-3*H*-1,3,4-benzotriazepine) (Table 3) in yields of about 50% [8] (Scheme 2). Thus, the thermolysis of 1- and 2-(*N*-arylbenzimidoyl)tetrazoles offers a convenient method to synthesize various 2,5-diaryl-3*H*-1,3,4-benzotriazepines.

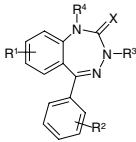
Several 2*H*-1,3,4-benzotriazepin-2-ones bearing complex 3-alkyl and 3-acyl substituents, including aromatic and hetero-aromatic partial structures, are described in the patent literature [9]. However, of the claimed compounds only the seven benzotriazepinones **13b–h** were characterized (Table 4).

These were obtained by substitution of the complete heterocycle **13a**, which was prepared similar to other 5-phenyl-1,3,4-benzotriazepin-5-ones [1], both by heating 2-(methylamino)benzophenone with hydrazine carboxylic acid ethyl ester and by intramolecular thermic cyclization of 2-(methylamino)benzophenon-semicarbazone. The further conversion of **13a** in dimethylformamide occurs at room temperature under an inert gas atmosphere. After sodium hydride has reacted, the reaction is achieved with the appropriate substituted benzoyl chlorides **13b–e** or benzyl bromides **13f–h**. The latter react much more faster and in better yields than the acyl chlorides (**13f**: 59% vs. **13b**: 27%) (Scheme 3).

For the purposes of biological testing, compounds **13b–h** (see 2.3.) were marked with either fluorescent agents and radioactive isotopes.

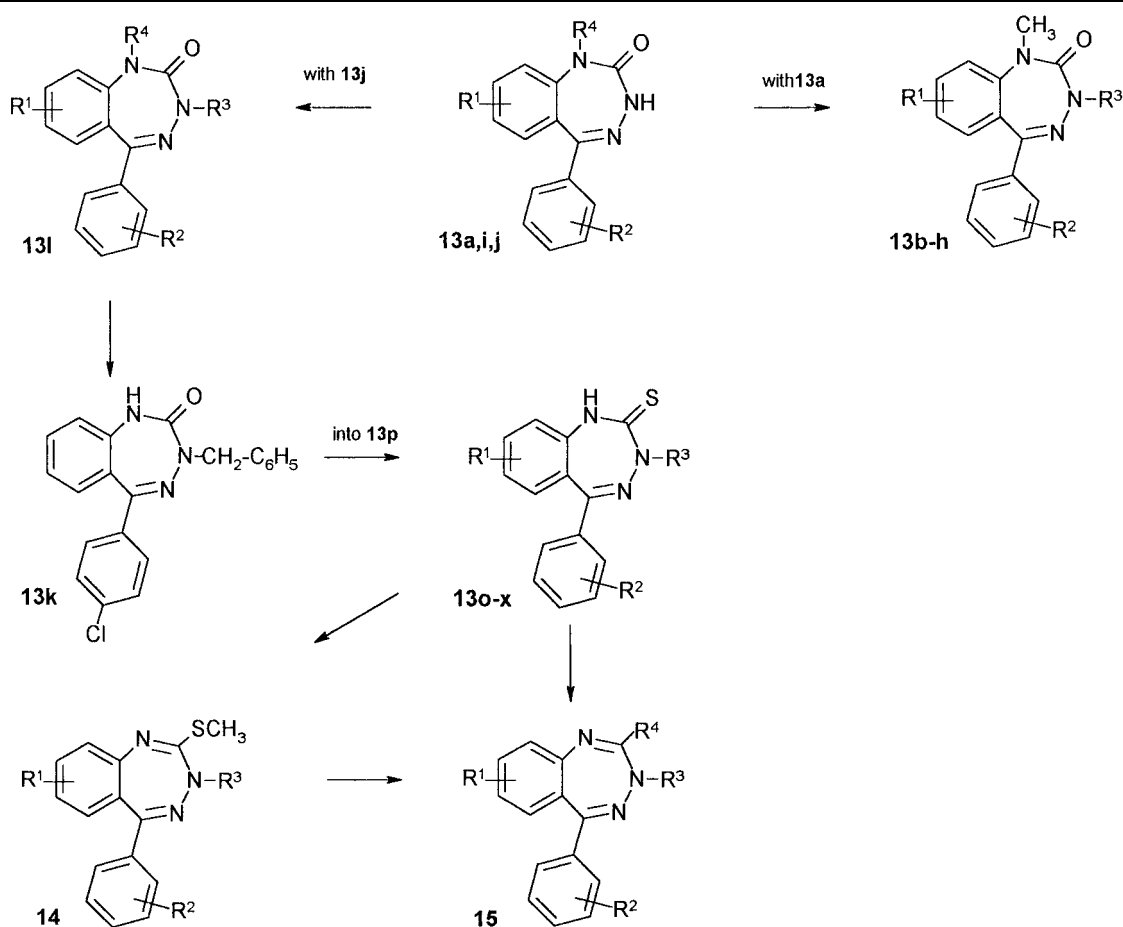
In addition to related thieno[2,3-*e*][1,2,4]triazepines, several 5-phenyl-1,3,4-benzotriazepin-2-ones and -thiones **13** are covered in the literature [31, 32]. The synthesis of **13i** was achieved analogously to **13a** by heating (180 °C) of

Table 4: 2-Oxo- and 2-thioxo-1,3,4-benzotriazepines

						
Compd.	X	R ¹	R ²	R ³	R ⁴	Ref.
13a	O	H	H	H	CH ₃	[9]
13b	O	H	H	(4-F–C ₆ H ₄)–CO	CH ₃	[9]
13c	O	H	H	(4-Cl–C ₆ H ₄)–CO	CH ₃	[9]
13d	O	H	H	(3,4-F ₂ –C ₆ H ₃)–CO	CH ₃	[9]
13e	O	H	H	(3,4-Cl ₂ –C ₆ H ₃)–CO	CH ₃	[9]
13f	O	H	H	(4-F–C ₆ H ₄)–CH ₂	CH ₃	[9]
13g	O	H	H	(4-Cl–C ₆ H ₄)–CH ₂	CH ₃	[9]
13h	O	H	H	(3,4-Cl ₂ –C ₆ H ₃)–CH ₂	CH ₃	[9]
13i	O	H	4-Cl	H	H	[31, 32]
13j	O	H	4-Cl	H	CH ₃ OCH ₂	[31, 32]
13k	O	H	4-Cl	C ₆ H ₅ CH ₂	H	[31, 32]
13l^b	O	H	4-Cl	C ₆ H ₅ CH ₂	CH ₃ OCH ₂	[31, 32]
13m^b	O	7-Cl	2-Cl	C ₂ H ₅ OCOCH ₂	(CH ₃) ₃ CCH ₂	[10]
13n	O	7-Cl	2-Cl	HOOC–CH ₂	(CH ₃) ₃ CCH ₂	[10]
13o	S	H	H	(4-CH ₃ O–C ₆ H ₄)CH ₂	H	[31, 32]
13p	S	H	4-Cl	C ₆ H ₅ CH ₂	H	[31, 32]
13q^c	S	H	4-Cl	(4-CH ₃ O–C ₆ H ₄)CH ₂	H	[31, 32]
13r	S	H	4-Cl	[3,4-(CH ₃ O) ₂ –C ₆ H ₃]CH ₂	H	[31, 32]
13s^a	S	H	4-Cl	3-pyridyl–CH ₂	H	[31, 32]
13t^b	S	H	4-Br	(4-CH ₃ O–C ₆ H ₄)CH ₂	H	[32]
13u	S	H	4-CH ₃	(4-CH ₃ O–C ₆ H ₄)CH ₂	H	[31, 32]
13v^b	S	H	4-COOC(CH ₃) ₃	(4-CH ₃ O–C ₆ H ₄)CH ₂	H	[32]
13w	S	7-Cl	H	(4-CH ₃ O–C ₆ H ₄)CH ₂	H	[31, 32]
13x	S	7-Cl	2-Cl	(4-CH ₃ O–C ₆ H ₄)CH ₂	H	[31, 32]
13y^b	S	7-NO ₂	H	(4-CH ₃ O–C ₆ H ₄)CH ₂	H	[31, 32]
13z	S	8-CH ₃	H	(4-CH ₃ O–C ₆ H ₄)CH ₂	H	[31, 32]
13zz^b	S	8-CH ₃	4-Cl	(4-CH ₃ O–C ₆ H ₄)CH ₂	H	[32]

^a as hydrochloride and as toluene 4-sulfonate in [31, 32]; ^b ¹H NMR data listed; ^c in [31] as hydrochloride

Scheme 3



2-amino-4'-chlorobenzophenone with hydrazine carboxylic acid ethyl ester in dimethylsulfoxide. The 1-methoxy-methyl derivative **13j** was formed selectively in dimethylformamide under mild conditions (no facts for a 3-substitution product) by reaction of **13i** with chloromethyl methyl ether in the presence of potassium hydroxide. In this way, the 1-position of the heterocyclic system was blocked in the course of the subsequent benzylation to **13l**, which was formed by using benzyl bromide in di-

methylsulfoxide at room temperature and in the presence of sodium hydride. Hydrolysis in hydrochloric acid removed the 1-substituent and **13k** was formed. Subsequent heating (100 °C) of **13k** with diphosphorpentasulfide in diethyleneglycol dimethyl ether provided **13p** (Scheme 3). Further 2-thio derivatives **13q–zz** were prepared in the known manner [1, 2] starting with the reaction of 2-isothiocyanatobenzophenones and benzylhydrazines followed by proton catalyzed cyclization of the formed thiosemicarbazide derivatives (Table 4). The methylthio derivatives **14** (Table 5) were synthesized by reacting iodomethane with **13** either in absolute dimethylformamide in the presence of sodium hydride (**14a, c–l**) or in acetone in the presence of potassium carbonate (**14b**) (Scheme 3).

The 2-hydrazino compounds **15** (Table 6) are accessible from both the analogous 2-thio derivatives **13** (in tetrahy-

Table 5: 2-Methylthio-5-aryl-3H-1,3,4-benzotriazepines

Compd.	R ¹	R ²	R ³	Ref.
14a ^a	H	H	(4-CH ₃ O-C ₆ H ₄)CH ₂	[31, 32]
14b ^a	H	4-Cl	(4-CH ₃ O-C ₆ H ₄)CH ₂	[31, 32]
14c	H	4-Cl	[3,4-(CH ₃ O) ₂ -C ₆ H ₃]CH ₂	[31, 32]
14d ^a	H	4-Cl	3-pyridyl-CH ₂	[31, 32]
14e ^b	H	4-Br	(4-CH ₃ O-C ₆ H ₄)CH ₂	[32]
14f ^a	H	4-CH ₃	(4-CH ₃ O-C ₆ H ₄)CH ₂	[31, 32]
14g ^b	H	4-COOC(CH ₃) ₃	(4-CH ₃ O-C ₆ H ₄)CH ₂	[32]
14h ^a	7-Cl	H	(4-CH ₃ O-C ₆ H ₄)CH ₂	[31, 32]
14i	7-Cl	2-Cl	(4-CH ₃ O-C ₆ H ₄)CH ₂	[31, 32]
14j ^a	7-NO ₂	H	(4-CH ₃ O-C ₆ H ₄)CH ₂	[31, 32]
14k ^a	8-CH ₃	H	(4-CH ₃ O-C ₆ H ₄)CH ₂	[31, 32]
14l ^b	8-CH ₃	4-Cl	(4-CH ₃ O-C ₆ H ₄)CH ₂	[32]

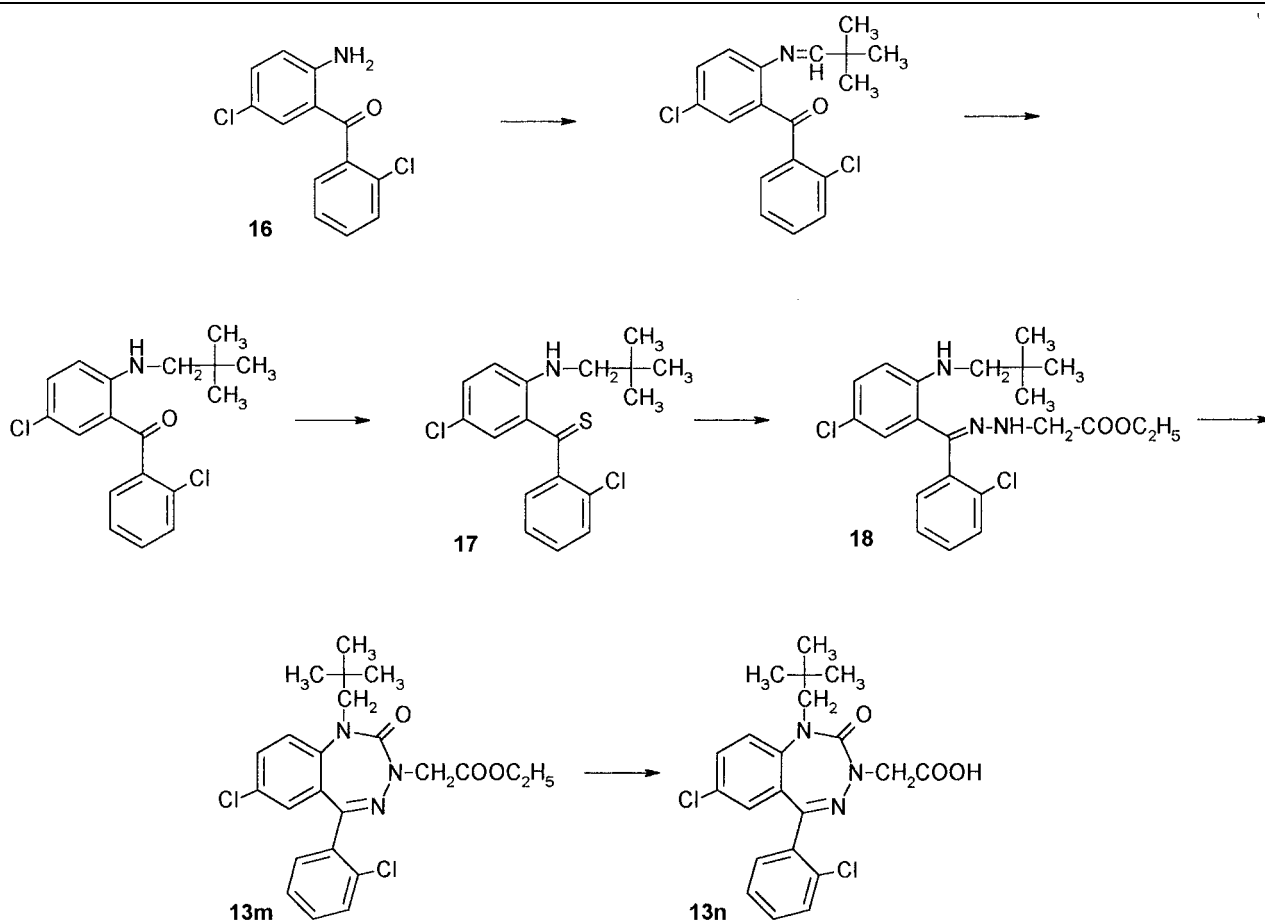
^a ¹H NMR data listed in [31, 32], ^b ¹H NMR data listed

Table 6: 2-Hydrazino-5-aryl-3H-1,3,4-benzotriazepines [31, 32]

Compd.	R ¹	R ²	R ³	R ⁴
15b ^a	H	4-Cl	C ₆ H ₅ CH ₂	H
15c	H	4-Cl	(4-CH ₃ O-C ₆ H ₄)CH ₂	H
15d	H	H	(4-CH ₃ O-C ₆ H ₄)CH ₂	CH ₃ CO
15e	H	4-Cl	[3,4-(CH ₃ O) ₂ -C ₆ H ₃]CH ₂	CH ₃ CO
15f	8-CH ₃	H	(4-CH ₃ O-C ₆ H ₄)CH ₂	CH ₃ CO

^a ¹H NMR data listed in [31, 32]

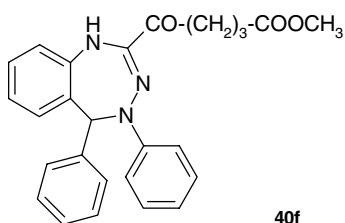
Scheme 4



drofurane; **15b, c**) by direct heating and the 2-methylthio derivatives **14** (in ethanol; **15c**) with hydrazine hydrate. The acetylhydrazino compounds **15d–f** are formed by heating the related 2-methylthio derivatives **14** with acetylhydrazine in *n*-butanol at 110 °C (Scheme 3).

The only 2-amino substituted 5-aryl-1,3,4-benzotriazepine mentioned in the patents [31, 32] is **15a**, which was prepared by heating **14b** and aminoacetaldehyde dimethyl acetal together in ethoxyethanol in the presence of *p*-toluene sulfonic acid (Scheme 14, 2.2.).

Among various other benzo- and thienocondensed, seven membered heterocycles the 1,3,4-benzotriazepin-3-ylacetic acid **13n** and the related ethyl ester **13m** (Table 4) are described in a patent (Scheme 4) [10]. Compound **17** is prepared starting from the reaction of **16** with pivalic aldehyde, subsequent reduction of the formed aldimine with sodium cyanoborohydride, and thionation with Lawesson's reagent. The reaction of the thioketone **17** with hydrazine acetic acid ethyl ester hydrochloride yields **18**. Compound **13m** is obtained by the reaction of **18** with triphosgene/triethylamine. The formed triazepine is saponified to **13n** with 1 M sodium hydroxide solution at room temperature.



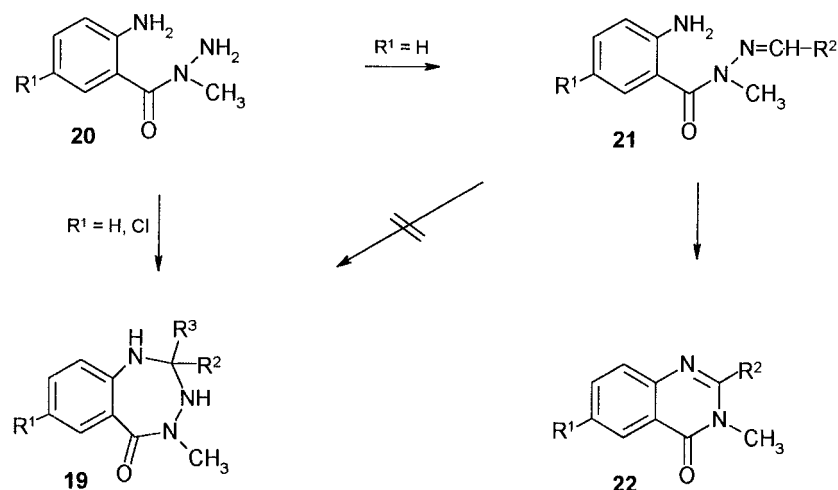
In addition to the 5-unsubstituted **40**, Froberg et al. [28, 29] unexpectedly obtained the 4,5-diphenyl-1,3,4-benzotriazepine **40f** by proton catalyzed reaction of 2-oxoadipic acid 6-methyl ester 1-*N*¹,*N*³-diphenylamidrazone **39a** (Scheme 12; R¹, R² = H) with benzaldehyde in ethanolic solution.

2.1.2. 1,3,4-Benzotriazepin-5-ones

In previous papers the authors occasionally have erroneously characterized ring-contracted side products, such as 1,3,4-oxadiazoles or quinazolines, instead of the desired 1,3,4-benzotriazepin-5-ones. This is reasonable on the one hand due to the existence of more than one reactive site of the starting compounds, on the other hand with the special tautomeric circumstances of this seven membered heterocyclic system [1, 2]. Since the publication of the second part of this review, several authors have published syntheses and structure elucidations of 1,3,4-benzotriazepin-5-ones; in the most cases attention was paid to the high instability of these compounds. However, with regard to the structures proposed in some publications there is a requirement for further structural investigations (signed with *).

To obtain the 2-monosubstituted 1,3,4-benzotriazepin-5-ones **19** Shailaja and Reddy [11] allowed 1-(2-aminobenzoyl)-1-methylhydrazine **20a** (R¹ = H) to react with various aldehydes (Scheme 5). Independently of nature and position of the substituents, the reaction with benzaldehydes always yields the arylidenehydrazines **21** [R² = (un)subst. phenyl], the formation of which was exemplarily verified by synthesis from isatoic acid anhydride

Scheme 5



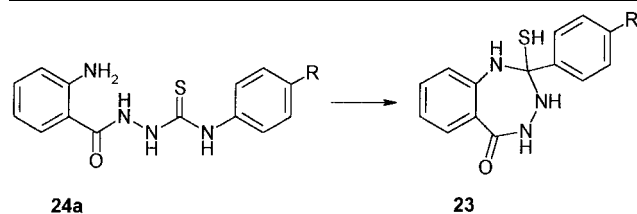
and *N*-(4-methoxybenzyliden)-*N'*-methylhydrazine. Only the aliphatic *n*-butyaldehyde provided a compound with a structure that was assigned as **19a** (Table 7). The authors' attempts to convert **21** into the desired products **19** by thermic intramolecular cyclization failed and the 2-substituted 3-methylquinazolin-4-ones **22** were isolated. However, there is another course of reaction in the case of dialkyl ketones, cycloalkanones, and methyl aryl ketones. Based on ^1H NMR data, the isolated reaction products were characterized as derivatives neither of **21** nor of **22**, but to be **19b–g** (Table 7).

Comprehending these results [11] with respect to decided structural investigations (see 2.3.), Pihlaja et al. [12] synthesized the further derivatives **19h–w** (Table 7) from **20a** ($\text{R}^1 = \text{H}$) and **20b** ($\text{R}^1 = \text{Cl}$), respectively, and several

acetophenones by proton catalyzed cyclocondensation of the reactants in benzene (Scheme 5).

Preparation of the 2-sulfanyl-2-arylamino derivatives **23a–d**^{*} (Table 8) is reported by Reddy et al. [13], who attempted to synthesize these compounds via proton catalyzed intramolecular cyclization of the related 1-(2-amino-benzoyl)-4-aryltiosemicarbazide **24a** (Scheme 6). The investigators most probably did not isolate the declared seven membered heterocycles.

Scheme 6

Table 7: 2,2-Disubstituted 5-oxo-1,3,4-benzotriazepines **19**

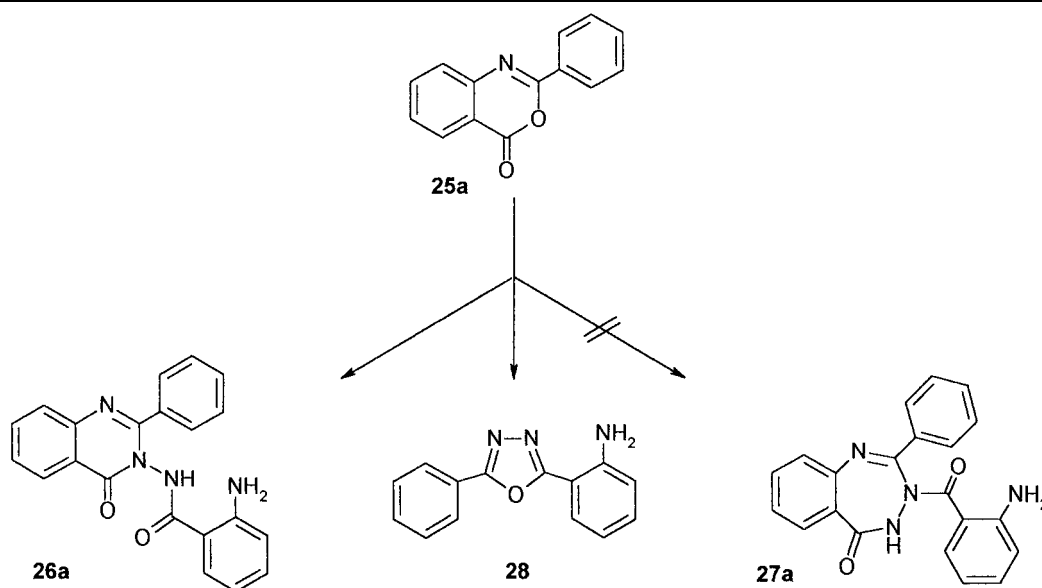
Compd.	R ¹	R ²	R ³	Ref.
19a	H	H	C ₃ H ₇	[11]
19b	H	CH ₃	CH ₃	[11, 12]
19c	H	C ₆ H ₅ CH ₂	C ₆ H ₅ CH ₂	[11]
19d	H	CH ₃	C ₆ H ₅	[11, 12]
19e	H	CH ₃	4-NO ₂ -C ₆ H ₄	[11, 12]
19f	H		-(CH ₂) ₄ -	[11]
19g	H		-(CH ₂) ₅ -	[11, 12]
19h	H	CH ₃	(CH ₃) ₂ CH	[12]
19i	H	CH ₃	(CH ₃) ₃ C	[12]
19j	H	CH ₃	4-CF ₃ -C ₆ H ₄	[12]
19k	H	CH ₃	3-Cl-C ₆ H ₄	[12]
19l	H	CH ₃	4-Br-C ₆ H ₄	[12]
19m	H	CH ₃	4-CH ₃ -C ₆ H ₄	[12]
19n	H	CH ₃	4-CH ₃ O-C ₆ H ₄	[12]
19o	Cl	CH ₃	CH ₃	[12]
19p	Cl	CH ₃	(CH ₃) ₃ C	[12]
19q	Cl	CH ₃	C ₆ H ₅	[12]
19r	Cl	CH ₃	4-NO ₂ -C ₆ H ₄	[12]
19s	Cl	CH ₃	4-CF ₃ -C ₆ H ₄	[12]
19t	Cl	CH ₃	3-Cl-C ₆ H ₄	[12]
19u	Cl	CH ₃	4-Br-C ₆ H ₄	[12]
19v	Cl	CH ₃	4-CH ₃ -C ₆ H ₄	[12]
19w	Cl	CH ₃	4-CHO ₃ -C ₆ H ₄	[12]

In another paper [14] Reddy and Reddy reported on the reaction of 2-phenyl-4*H*-3,1-benzoxazin-4-one (**25a**) with 2-aminobenzoyl hydrazine in boiling pyridine; the column chromatographic separation yielded two different products. The main product was identified to be the quinazolinone **26a**, whereas the second compound obtained in a smaller amount (28%) was thought to be the 3-(2-amino-benzoyl)-1,3,4-benzotriazepin-5-one **27a**. Subsequently, the authors recognized that this was incorrect [15] and reinterpreted their results to allow for an elimination of one mole anthranilic acid. This reaction mechanism pro-

Table 8: 2-Arylsulfanyl 2-sulfanyl-5-oxo-1,3,4-benzotriazepines **23** [13]

Compd.	R
23a	H
23b	Br
23c	Cl
23d	CH ₃

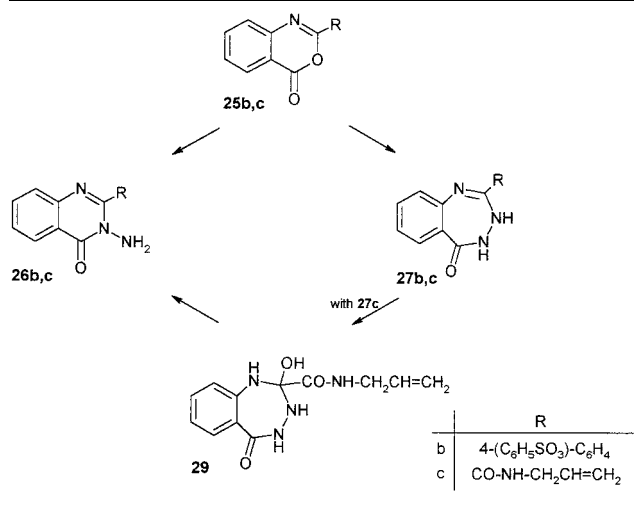
Scheme 7



vides in addition to **26a** the oxadiazole **28** instead of **27a** (Scheme 7). To prove this fact, **28** was prepared by opposite synthesis starting from *N*-(2-nitrobenzoyl)-*N'*-benzoylhydrazine.

Habib et al. [16] studied the influence of hydrazine hydrate on the 2-[4-(benzenesulfonyloxy)phenyl]-3,1-benzoxazin-4-one **25b**. Depending on the solvent used, a different course of reaction was observed upon heating. In absolute ethanol the 3-aminoquinazolin-4-one **26b** was formed; with dry xylene a different compound was isolated. On the basis of the IR and ^1H NMR spectra the latter was proposed to be the 1,3,4-benzotriazepine **27b*** (Scheme 8). Comparing the few spectral data with those of the 2-(2-aminophenyl)-5-phenyl-1,3,4-oxadiazole **28**, which is unsubstituted at the 2-aryl ring [17], the structure given for **27b** is probably incorrect. Moreover, the behavior upon heating the authentic 2-phenyl-4,5-dihydro-3*H*-1,3,4-benzotriazepin-5-one in xylene is not consistent with structure **27b** because **28** thereby is formed in good yield [17].

Scheme 8



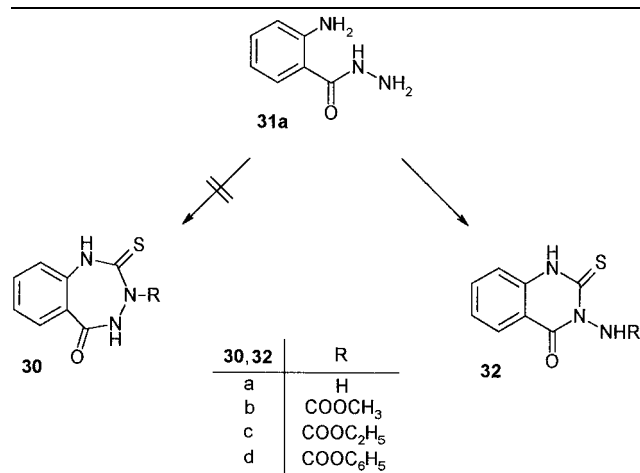
Korkodinova et al. [18] also published a work on the formation of a 1,3,4-benzotriazepine **27c***, obtained by the reaction of hydrazine hydrate with the 3,1-benzoxazin-4-

one **25c** in absolute ethanol. This cinetically controlled reaction occurs under mild conditions. However, in 96% ethanol, **27c**, which should be formed in the first stage, adds one mole of water. Therefore, in the opinion of the authors compound **29*** was the final product. If the same reaction was carried out in dimethylformamide at 150 °C, a thermodynamic control of process provides the analogous 3-aminoquinazoline **26c**. This product was also obtained by melting (at about 140 °C) **27c** and **29** for a short time (1–2 min) (Scheme 8).

Nawrocka et al. reported [19] the preparation of the 2-thioxo-1,3,4-benzotriazepine-5-ones **30***. The authors describe the synthesis of the core compound **30a** from anthranilic acid hydrazide **31a** and carbon disulfide by refluxing an ethanolic reaction mixture for 25 h in the presence of sodium hydroxide. In this way, the synthesis of related pyrido[2,3-*e*][1,2,4]benzotriazepines from 2-aminonicotinic acid hydrazide was also possible. With respect to both the known instability of 3,4-unsubstituted 1,3,4-benzotriazepin-5-ones [1, 2] and the results reported by Davidson [20], it is rather impossible that these products possess a benzotriazepine structure. Davidson demonstrated that the desired 1,3,4-benzotriazepin-2,5-diones are not formed from anthranilic acid hydrazide even under mild conditions. Instead of these, the 1,3,4-oxadiazoles, which are subsequently converted into quinazolin-2,4-diones at higher temperatures, are formed at the first stage of the reaction. Comparing the IR and ^1H NMR data listed for **30a** with that of the authentic 3-amino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one [21] and the report of Sunder and Peet [22] on the influence of carbon disulfide on an anthranilic acid hydrazide, compound **30a** considered to be the 2-thioxo-1,3,4-benzotriazepin-5-one has to be characterized as **32a**. For this reason, the compounds obtained from “**30a**” and various chloroformic acid esters also did not represent the 1,3,4-benzotriazepin-3-ylcarboxylic acid esters **30b–d**. Based on the ^1H NMR data, these products most probably are the 3-aminosubstituted 2-thioxo-1,2,3,4-tetrahydroquinazolin-4-ones **32b–d** (Scheme 9).

Karp demonstrated impressively that the substitution pattern determines the course of the cyclization of the anthranilic acid hydrazides used [23, 24]. He performed various reactions with the compounds **31b–c**, which were pre-

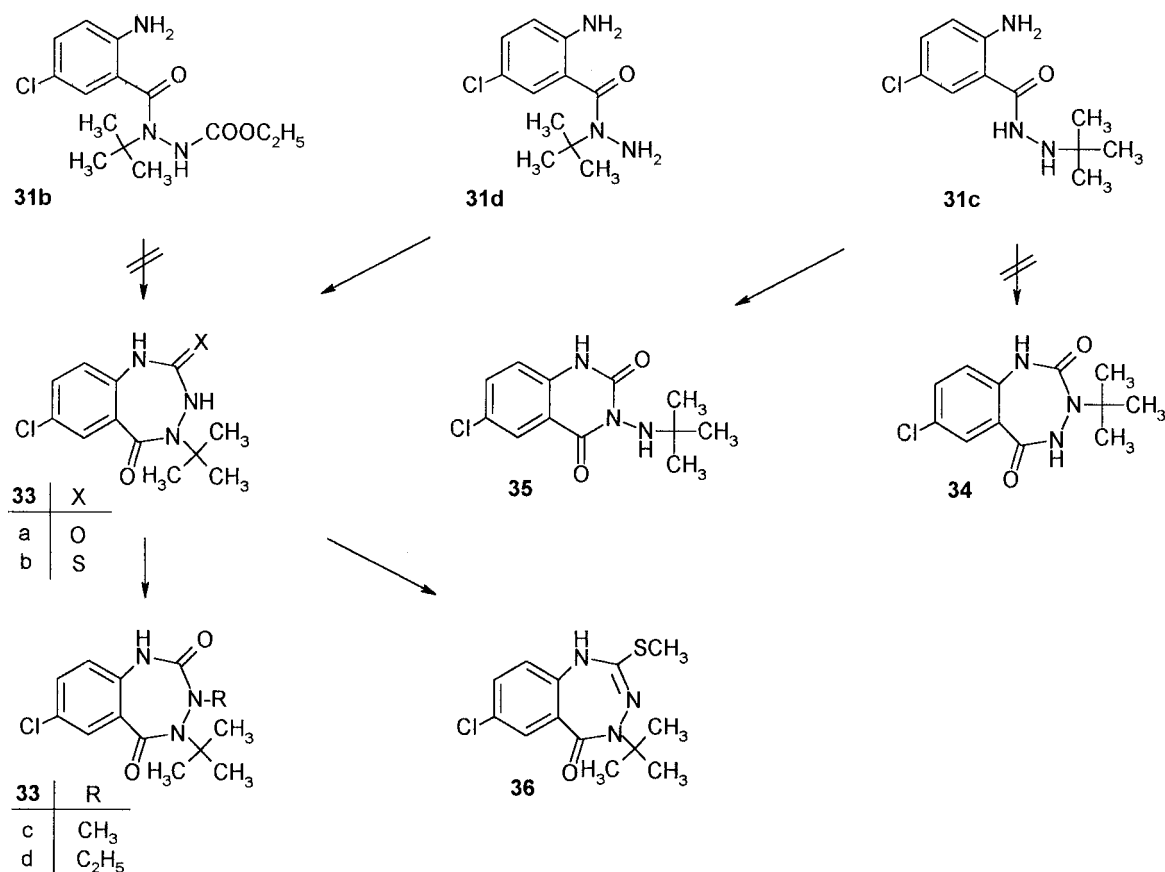
Scheme 9



pared from 2-nitro-5-chlorobenzoyl chloride under various cyclization conditions. As a result of the reduced reactivity of the carbonyl and aromatic amino group of **31**, both the proton/base catalyzed and the thermic cyclizations to **33a** failed. With regards to the discussion about the reaction of **31c** [19] (the two hydrazide nitrogen atoms are not completely substituted) with chloroformic acid trichloro-methyl ester at room temperature also did not provide the 1,3,4-benzotriazepine **34** but rather the 3-*tert*.butylaminoquinazolin-2,4-dione **35**.

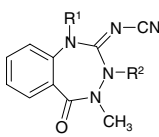
In contrast, the 1,3,4-benzotriazepine derivatives **33a, b** were formed under mild conditions and in the presence of triethylamine under the influence either of chloroformic acid trichloromethyl ester or thiophosgene on **31d** (Scheme 10).

Scheme 10

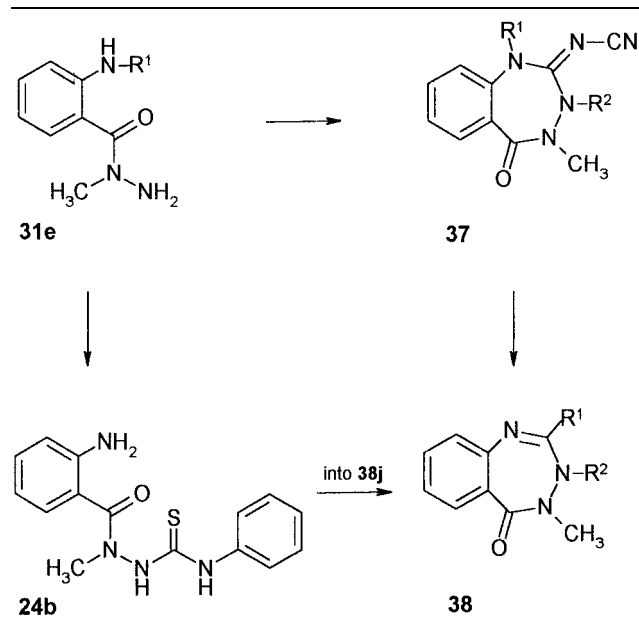


Preparation of the 2-cyanimino-5-oxo derivatives **37** claimed in a patent [25] is in accordance with these results. However, the data used for structural analysis are not given. The products **37b–f** are formed upon heating **37a** in dimethylformamide with halogen compounds in the presence of potassium hydrogen carbonate/potassium iodide. On the other hand, **37a** is formed by cyclization of the related **31e** with cyanoiminodithiocarboxylic acid dimethyl ester in boiling propan-1-ol (24 h) (Scheme 11, Table 9). With the exception of **38f** and **38j**, compounds **37** represent starting materials for the 2-aminosubstituted 1,3,4-benzotriazepin-5-ones **38** (Table 10, Scheme 11). Depending on the reaction conditions the amino derivatives **38a–i**, **38k, l**, and **38m–t** are formed. Thus, upon heating **38** for 24 h in propan-1-ol with a 15molar excess of a primary or secondary amine, the cyanimino group is replaced by the appropriate amino group to form **38a–i**; **38k, l**. On the

Table 9: 2-Cyanimino-5-oxo-1,3,4-benzotriazepines [24]

		
Compd.	R ¹	R ²
37a	H	H
37b	H	(2-pyridyl)-CH ₂
37c	H	(3-pyridyl)-CH ₂
37d	H	TMPCOO(CH ₂) ₃
37e	H	[4-(C ₆ H ₅)-piperazin-1-yl]-(CH ₂) ₃
37f	CH ₃ –CH ₂ –CH(CH ₃)	(2-pyridyl)-CH ₂

Scheme 11



other hand, if cyclic amines such as piperidine, 1,4-diazepane, and 1-phenylpiperazine are allowed to react in a half molar ratio with the related **37** in refluxing benzene, the addition of the amine to the cyano group occurs rapidly (1.5 h). Because of the small yield of compounds **38m–t** the sparingly soluble, nonreacted **37** was filtered off and allowed to react again. The 3-acyl derivative **38f** was prepared in a chloroform-pyridine mixture under mild conditions from **38e** by acylation with nicotinoyl chloride. To synthesize **38j** a method for 4-unsubstituted 2-phenylamino-4,5-dihydro-3*H*-1,3,4-benzotriazepin-5-one from Omar

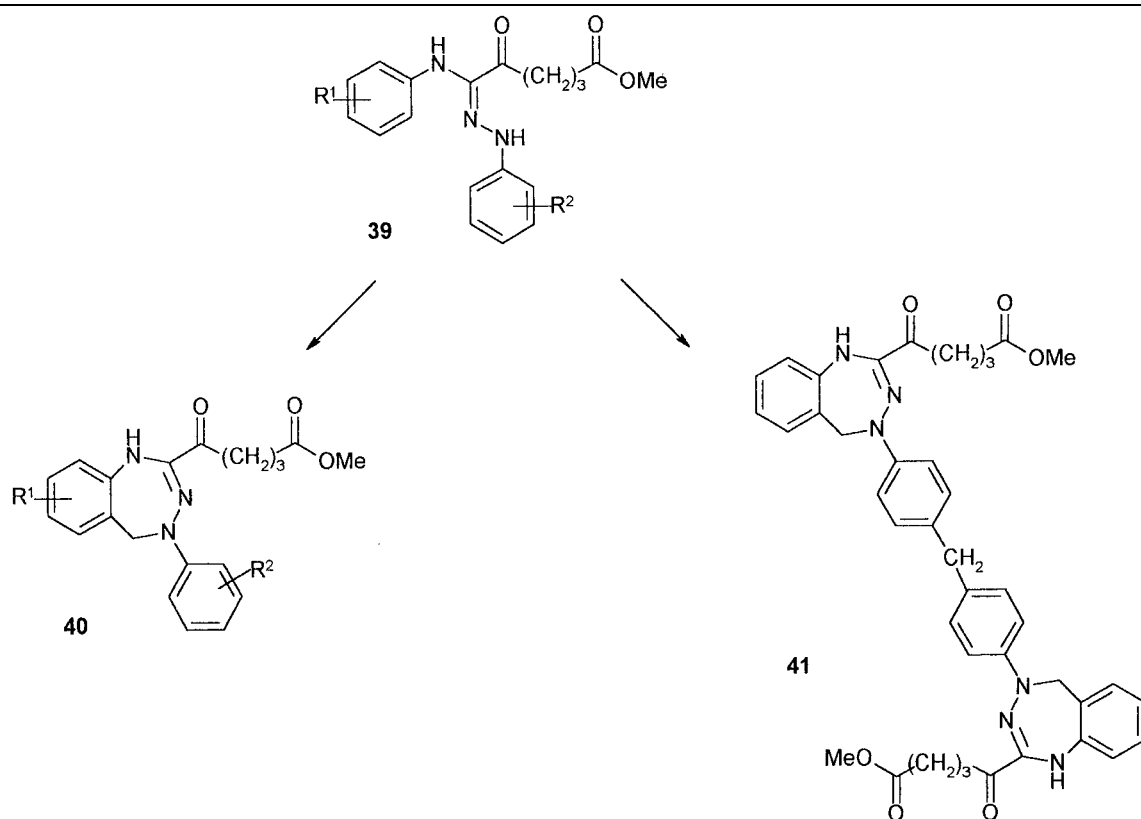
Table 10: 2-Aminosubstituted 5-oxo-1,3,4-benzotriazepines [24]

Compd.	R ¹	R ²
38a	(CH ₃) ₂ CH–CH ₂ NH	H
38b	(CH ₃) ₂ CH–CH(CH ₃)–NH	H
38c	(CH ₃) ₃ C–CH(CH ₃)–NH	H
38d	(CH ₃) ₃ C–CH(CH ₃)–NH	(2-pyridyl)–CH ₂
38e	C ₆ H ₅ CH ₂ NH	H
38f	C ₆ H ₅ CH ₂ NH	nicotinoyl
38g	(2-pyridyl)–CH ₂ NH	H
38h	(3-pyridyl)–CH ₂ NH	H
38i^a	(3-pyridyl)–CH ₂ NH	[4-(C ₆ H ₅)-piperazin-1-yl]–(CH ₂) ₃
38j	C ₆ H ₅ NH	H
38k	piperidino	H
38l	4-(C ₆ H ₅)-piperazin-1-yl	H
38m	(CH ₃) ₃ C–CH(CH ₃)–NH–C(NH ₂)=N	H
38n	piperidino–C(NH ₂)=N	H
38p	piperidino–C(NH ₂)=N	(2-pyridyl)–CH ₂
38q	piperidino–C(NH ₂)=N	(3-pyridyl)–CH ₂
38r	(1,4-diazepam-1-yl)–C(NH ₂)=N	TMPCOO(CH ₂) ₃
38s	[4-(C ₆ H ₅)-piperazin-1-yl]–C(NH ₂)=N	H
38t	(4-pyridyl)–CH ₂ –N(CH ₃)–C(NH ₂)=N	(2-pyridyl)–CH ₂

^a as base and as hydrochloride

et al. [26] was used. This compound was formed by heating the thiosemicarbazide **24b** with 1,3-dicyclohexyl carbodiimide in benzene. Whereas the cyclodesulfurization of the 1-(2-aminobenzoyl)-4-phenylthiosemicarbazide, which

Scheme 12

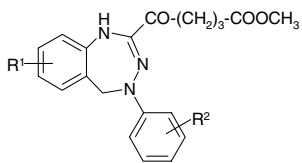


was carried out under the conditions described in [26], provided the 1,3,4-oxadiazole **28** (Scheme 7) [27], the formation of a ring-contracted alternative product is prevented by the methyl group of **24b** (Scheme 11).

2.1.3. 5-Unsubstituted 1,3,4-benzotriazepines

In connection with their studies on the cyclization of N^1 -aryl substituted amidrazones with aldehydes and carboxylic acid chlorides yielding 1,2,4-triazoles and Δ^2 -1,2,4-triazolines, respectively, Froberg et al. [28, 29] have also studied reactions with the 2-oxoadipic acid 6-methyl ester 1- N^1,N^3 -diarylamidrazones **39**. In this case, the authors observed a reaction course which was different from that for the transformation of the N^3 -alkylated or N^3 -unsubstituted amidrazones. Thus, the 4,5-dihydro-1*H*-1,3,4-benzotriazepines **40a–e** (Table 11) were formed from the related **39** with the 1.5 fold excess of formaldehyde in ethanolic solution, involving the N^3 -phenyl moiety. When the reaction was done with benzaldehyde, the 5-phenyl derivative **40f** (see page 875) was isolated. However, these compounds could only be obtained if the N^3 -phenyl substituent was not occupied in either 2- or 6-position. Otherwise, the reaction yields 1,4-disubstituted Δ^2 -1,2,4-triazolines [28]. If the solvent was changed from ethanol to acetic acid, the reaction of **39a** ($R^1, R^2 = H$) with formaldehyde provided bis[4-(1,3,4-benzotriazepin-4-yl)phenyl]methane **41** as the main product. The formation of **41** was explained by the presence of an excess of formaldehyde (Scheme 12).

Table 11: 5-Unsubstituted 4-aryl-1,3,4-benzotriazepines [28, 29]

		
Compd.	R^1	R^2
40a	H	H
40b	H	4-Cl
40c	7-Cl	H
40d	7-Cl	4-Cl
40e	9-CH ₂ OH	H

Regarding the mechanism of this reaction, the authors excluded an initial attack of the aldehyde to the N^3 -aryl ring. Nevertheless, they could not ascertain whether the formaldehyde reacts first with the N^1 -nitrogen of the amidrazone structure or whether the cyclization occurs by another mechanism [29].

Stankovsky et al. [30] reported the synthesis of several 3,4-diacyl-1,3,4-benzotriazepines **42*** (Table 12). These compounds should be formed in good yields by reaction

Scheme 13

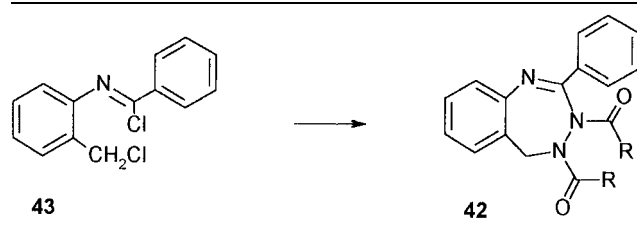
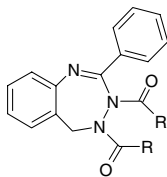


Table 12: 5-Unsubstituted 3,4-diacyl-2-phenyl-1,3,4-benzotriazepines [30]

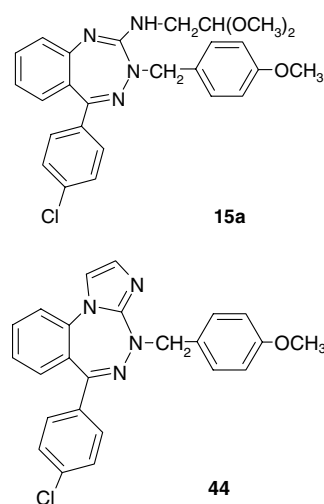
	
Compd.	R^1
42a	CH ₃
42b	C ₆ H ₅
42c	C ₂ H ₅ O

of *N*-(2-chloromethylphenyl)-benzimidoyl chloride **43** with the sodium salts of the related acyl hydrazines. In contrast, the direct use of acyl hydrazines resulted in only small amounts of **42**. The starting compound **43** was prepared from *N*-(*o*-tolyl)-benzamide in two steps by chlorination (1. thionylchloride, 2. sulfonylchloride) (Scheme 13). The questionable (printing errors) publication contains no experimental data; thus, it is impossible to independently check the soundness of the arguments for the assigned structures **42a–c**.

2.2. Syntheses of heterocyclic anellated 1,3,4-benzotriazepines

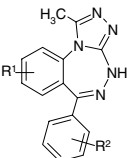
2.2.1. a-Anellated 1,3,4-benzotriazepines

In addition to several related 1,4-benzodiazepines and thieno[2,3-*e*][1,2,4]triazepines, a variety of a-anellated 1,3,4-benzotriazepines is claimed in two patents [31, 32], which comprise the [1,2,4]triazolo[4,3-*a*][1,3,4]benzotriazepines **45–56** (Scheme 15, Tables 13–20) modified mainly in 4-position, but also the imidazolo[1,2-*a*] derivative **44**. The preparation of the latter was realized by thermic cyclization of **15a** in a hydrochloric acid – acetic acid mixture (Scheme 14), and the formation of **44** was verified by means of the ¹H NMR data.



The syntheses of the triazolo[4,3-*a*] derivatives have been reported with many examples in the patent literature [31, 32] by way of the synthetic routes shown in Scheme 15. Acting as partly ring-opened starting materials, the 2-methylthio and the 2-hydrazino derivatives **14** (Table 5) and **15** (Table 6), respectively, and the 2-(1,2,4-

Table 13: 4-Unsubstituted 6-aryl-1-methyl-[1,2,4]triazolo[4,3-a][1,3,4]benzotriazepines

				
Compd.	R ¹	R ²	Ref.	
45a	H	H	[31, 32]	
45b	H	4-Cl	[31, 32]	
45c^a	H	4-Br	[32]	
45d	H	4-CH ₃	[31, 32]	
45e^a	H	4-COOH	[32]	
45f	H	4-COOCH ₃	[32]	
45g^b	8-Cl	H	[31, 32]	
45h	8-Cl	2-Cl	[31, 32]	
45i	8-NO ₂	H	[31, 32]	
45j	9-CH ₃	H	[31, 32]	
45k^a	9-CH ₃	4-Cl	[32]	

^a ¹H NMR data listed; ^b base and hydrobromide in [31, 32]

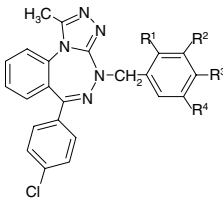
triazol-4-yl)-4'-chlorobenzophenone **57** were employed. Thus, the formation of the related **47h, i** (Table 14) and **50a** (Table 15) takes place in refluxing toluene by proton catalyzed cyclization of the acetyl hydrazino derivatives **15d–f**. Compounds **46a** and **47h** (Table 14) are synthesized directly in refluxing toluene from **15b, c** (Table 6) and orthoacetic acid triethyl ester. The proton catalyzed reaction of the 2-methylthio heterocycles **14** with acetylhydrazine yields the triazolo derivatives **49c, e, f, u–w**, **50c** (Table 15), and **51d** (Table 16), respectively.

Key importance in the synthesis of the 4-substituted [1,2,4]triazolo[4,3-a][1,3,4]benzotriazepines is given to the 4-unsubstituted **45** (Table 13). Compound **45b** was obtained from an ethanolic solution of **57** and hydrazine sulfate-sodium acetate upon refluxing for 160 h under a nitrogen gas atmosphere. On the other hand, if a mixture of trifluoroacetic acid and sulfuric acid reacts with **47i** in the presence of anisole under mild conditions (Table 14), **45b** is obtained in a much more convenient manner via removal of the 4-substituent. In a similar fashion, **47** are debenzylated in 4-position either by a hydrobromic acid – acetic acid mixture in the presence of anisole or by heating (70 °C) in methanesulfonic acid resulting in compounds **45a, c, d, g–k** [31, 32] and **45e, f** [32] (Scheme 15), respectively.

To synthesize most of the compounds **46–53** listed in Tables 14–17, the reverse route was taken. As a rule, compounds with the general structure **45** react with the related substituted alkyl-, aryl-, and heteroaryl-methyl halogenides in the presence of potassium hydroxide, potassium carbonate, sodium hydride or rarely (**49s**) lithium bis(trimethylsilyl) amide under mild conditions in absolute dimethylformamide and under an argon gas atmosphere.

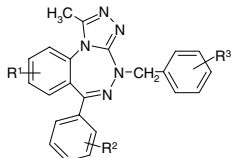
Among these compounds is **52q**, which results in the reaction of **45b** with bromoacetic acid ethyl ester. The mild saponification of **52q** with sodium hydroxide yields the free acid **52r** (Table 17). The latter represents the starting compound for the 4-carbamoylmethyl substituted derivatives **54a–i** (Table 18), which are prepared in absolute dimethylformamide at about –15 °C. In order to synthesize the **54**, **52r** is firstly activated by the reaction of chloroformic acid isobutyl ester – triethylamine, and then transformed with the appropriate primary amines in a second step.

Table 14: 4-Benzylated 6-(4-chlorophenyl)-1-methyl-[1,2,4]triazolo[4,3-a][1,3,4]benzotriazepines [31, 32]

				
Compd.	R ¹	R ²	R ³	R ⁴
46a	H	H	H	H
46b	F	H	H	H
46c	H	F	H	H
46d	H	H	F	H
46e	F	H	F	H
46f	F	H	H	F
46g	H	F	H	F
46h	H	F	F	H
46i	Cl	H	H	H
46j	H	Cl	H	H
46k	H	H	Cl	H
46l^c	H	Cl	Cl	H
46m	NO ₂	H	Cl	H
46n	H	NO ₂	H	H
46o^a	H	H	NO ₂	H
46p^a	H	NO ₂	H	NO ₂
46q	H	H	OH	H
46r^a	H	OH	OH	H
46s	H	H	NH ₂	H
46t	H	H	COOH	H
46u	CN	H	H	H
46v^a	H	CN	H	H
46w	H	H	CN	H
46x	CH ₃	H	H	H
46y	H	CH ₃	H	H
46z	H	H	CH ₃	H
47a	H	H	C(CH ₃) ₃	H
47b	H	H	C ₆ H ₅	H
47c	CF ₃	H	H	H
47d	H	CF ₃	H	H
47e	H	H	CF ₃	H
47f	CH ₃ O	H	H	H
47g	H	CH ₃ O	H	H
47h^a	H	H	CH ₃ O	H
47i	CH ₃ O	H	H	CH ₃ O
47j	CH ₃ O	H	H	CH ₃ –CO
47k	CH ₃ O	H	H	NO ₂
47l	H	CH ₃ O	CH ₃ O	H
47m	H	CH ₃ O	CH ₃ O	CH ₃ O
47n	H	NO ₂	CH ₃ O	H
47o	H	Cl	CH ₃ O	H
47p	H	Cl	CH ₃ O	Cl
47q	H	CH ₃	CH ₃ O	H
47r	H	H	CF ₃ O	H
47s^a	H	H	C ₂ H ₅ O	H
47t	H	H	C ₆ H ₅ CH ₂ O	H
47u^a	H	C ₆ H ₅ CH ₂ O	C ₆ H ₅ CH ₂ O	H
47v	H	O–CH ₂ –O	O–CH ₂ –O	H
47w	Cl	H	O–CH ₂ –O	O–CH ₂ –O
47x^b	H	H	(CH ₃) ₂ N	H
47y	H	H	H–CONH	H
47z	H	H	CH ₃ CONH	H
48a	H	H	CH ₃ SO ₂ NH	H
48b	H	H	(CH ₃ SO ₂) ₂ N	H
48c^a	H	H	CH ₃ SO ₂	H
48d	H	H	CH ₃ O–CO	H

^a ¹H NMR data listed in [31, 32]; ^b in [31, 32] as hydrochloride; ^c in [32] only

Table 15: 6-Aryl-4-benzyl-1-methyl-[1,2,4]triazolo[4,3-a][1,3,4]-benzotriazepines

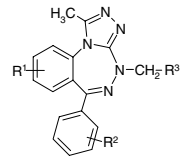
				
Compd.	R ¹	R ²	R ³	Ref.
49a ^b	H	H	4-CN	[32]
49b	H	H	4-CH ₃ O	[31, 32]
49c ^b	H	4-Br	4-CH ₃ O	[32]
49d ^a	H	4-CH ₃	3-CN	[31, 32]
49e	H	4-CH ₃	4-CH ₃ O	[31, 32]
49f ^b	H	4-[(CH ₃) ₃ C-O-CO]	4-CH ₃ O	[32]
49g	H	4-Br	4-Br	[32]
49h	H	4-NO ₂	4-Cl	[32]
49i ^c	H	4-NH ₂	4-Cl	[32]
49j ^{b,c}	H	4-NH ₂	4-NO ₂	[32]
49k ^{b,c}	H	4-NH ₂	4-CN	[32]
49l ^b	H	4-[(CH ₃) ₃ C-O-CONH]	4-Cl	[32]
49m ^b	H	4-[(CH ₃) ₃ C-O-CONH]	4-NO ₂	[32]
49n ^b	H	4-[(CH ₃) ₃ C-O-CONH]	4-CN	[32]
49o	H	4-COOH	4-Cl	[32]
49p ^b	H	4-COOH	4-NO ₂	[32]
49q	H	4-COOH	4-CN	[32]
49r	H	4-CH ₃ O-CO	4-Cl	[32]
49s ^b	H	4-CH ₃ O-CO	4-NO ₂	[32]
49t	H	4-CH ₃ O-CO	4-CN	[32]
49u	8-Cl	H	4-CH ₃ O	[31, 32]
49v	8-Cl	2-Cl	4-CH ₃ O	[31, 32]
49w ^a	8-NO ₂	H	4-CH ₃ O	[31, 32]
49x	9-CH ₃	H	3,4-Cl ₂	[32]
49y	9-CH ₃	H	3-CN	[32]
49z	9-CH ₃	H	4-CN	[31, 32]
50a	9-CH ₃	H	4-CH ₃ O	[31, 32]
50b	9-CH ₃	4-Cl	4-CN	[32]
50c ^b	9-CH ₃	4-Cl	4-CH ₃ O	[32]

^a ¹H NMR data listed in [31, 32]; ^b ¹H NMR data listed; ^c as hydrochloride

Starting from **45b** synthesis of the 4-oxoalkyl derivatives (Table 19) occurs either by 4-substitution with related halogen compounds (see above; **55b–d**) or by heating in an ethanolic formaldehyde solution for several days (**55a**). Compound **55e**, an 4-aminoalkyl derivative, is obtained by the aminomethylation of **45b**.

The acyl products **56b–k** listed in Table 20 were synthesized in various manners. For example, the reaction of **45b** with isocyanates in acetonitrile in the presence of sodium hydroxide provides the 4-carbamoyl heterocycles **56j, k**. The compounds **56a, h, i** were formed directly from **45b** by 4-acylation with related carboxylic acid halogenides under ice-cooling in a dichloromethan – pyridine

Table 16: 4-Heteroarylalkyl-substituted 6-aryl-1-methyl-[1,2,4]triazolo[4,3-a][1,3,4]benzotriazepines

				
Compd.	R ¹	R ²	R ³	Ref.
51a	H	H	3-pyridyl	[31, 32]
51b	H	H	4-pyridyl	[32]
51c	H	4-Cl	2-pyridyl	[31, 32]
51d ^{a,b}	H	4-Cl	3-pyridyl	[31, 32]
51e ^a	H	4-Cl	4-pyridyl	[31, 32]
51f ^d	H	4-Cl	1-oxido-3-pyridyl	[32]
51g	H	4-Cl	3-indolyl-CH ₂	[31, 32]
51h	H	4-Cl	(2-CH ₃ -4-thiazolyl)	[31, 32]
51i	H	4-Cl	(5-Cl-2-thienyl)	[31, 32]
51j	H	4-Cl	[3,5-(CH ₃) ₂ -4-isoxazolyl]	[31, 32]
51k ^a	H	4-Cl	(2-CH ₃ O-C ₆ H ₄)[(2-tetrahydro-pyran-yl)-oxy]CH	[31, 32]
51l ^d	H	4-Cl	C ₆ H ₅ -CH ₂ -(2-tetrahydro-pyran-yl)-oxy]CH	[31, 32]
51m	H	4-Cl	(3-indolyl)-CH ₂ -CH ₂	[31, 32]
51n	H	4-Cl	2,6-Cl ₂ -4-pyridyl	[31, 32]
51o ^a	H	4-Cl	3,5-Cl ₂ -4-pyridyl	[31, 32]
51p	H	4-CH ₃	4-pyridyl	[31, 32]
51q ^a	8-Cl	H	3-pyridyl	[31, 32]
51r ^{a,c}	8-Cl	H	4-pyridyl	[31, 32]
51s	8-NO ₂	H	3-pyridyl	[31, 32]
51t	8-NO ₂	H	4-pyridyl	[31, 32]
51u	9-CH ₃	H	3-pyridyl	[31, 32]
51v	9-CH ₃	H	4-pyridyl	[31, 32]
51w	8-Cl	2-Cl	3-pyridyl	[31, 32]
51x ^a	8-Cl	2-Cl	4-pyridyl	[31, 32]
51y ^d	8-Cl	2-Cl	1-oxido-3-pyridyl	[32]

^a ¹H NMR data listed in [31, 32]

^b in [31, 32] also as hydrochloride (¹H NMR data), citrate (¹H NMR data), dimesylate, p-toluene sulfonate (¹H NMR data), and sesqui benzene sulfonate

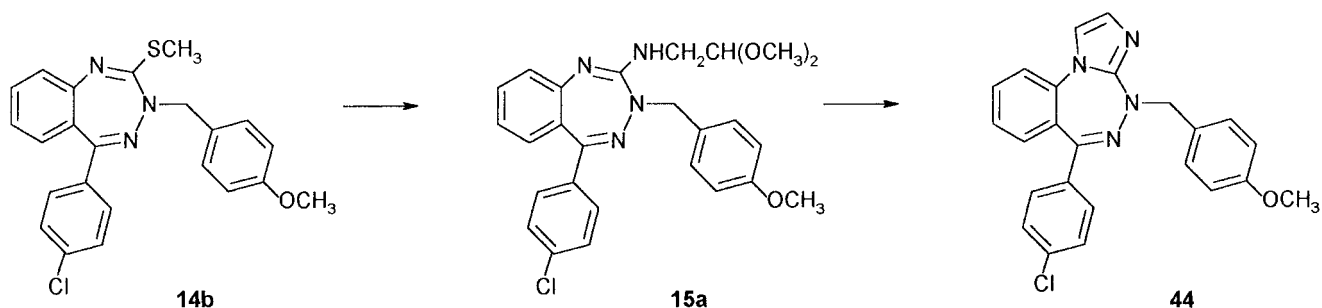
^c in [31, 32] also as hydrochloride (¹H NMR data) and p-toluene sulfonate (¹H NMR data)

^d ¹H NMR data listed

mixture. In either boiling ethanol or dichloromethan and in the presence of triethylamine, the reaction of **56a** with amines and thiophenol results in the 4-glycyl substituted 1,3,4-benzotriazepines **56b–f** and the 4-(S-phenylthioglycolyl) derivative **56g**, respectively.

Further derivatives of [1,2,4]triazolo[4,3-a][1,3,4]benzotriazepines were synthesized starting from the intact heterosystems by modification of the substituents in the 4- and 6-position [31, 32]. For example, the hydrogenolysis of **47t, u** yielded **46q, r**, and the reaction of **46q** with diazoethane resulted in the formation of **47s** (Table 14). Re-

Scheme 14



duction of the 4-(4-nitrobenzyl) derivative **46o** with palladium black in a methanol – formic acid mixture provided both **46s** and **47y**, which were then separated by column chromatography. Again, **46s** was used as starting compound for the *N*-acylamino products **47z** and **48a, b** both of which were synthesized by reaction with acetyl chloride and methansulfonyl chloride – triethylamine, respectively (Table 14). The oxidation products **52v, w** (Table 17) were formed in dichloromethane from **52t, u** by mild influence of some pyridinium salts of chromic acid. Whereas the starting material **52t** was formed from **45b** and styrene oxide in the presence of sodium hydride, **52u** resulted upon pyridinium *p*-toluene sulfonate catalyzed ethanolysis of **51t** (Table 16). In the same way, the preparation of **52x–z** and **53a–c** (Table 17) occurs by way of the analogous hydroxy derivatives, which were not characterized in detail [31, 32]. By oxidation of **51d** and **51w** with 3-chloroperbenzoic acid in ice-cooled, absolute dichloromethane, followed by a column chromatographic workup, the *N*-oxides **51f** and **51y**, respectively, were received.

Saponification of the ester group of the 6-substituents of **49r–t** at 50 °C or on heating (100 °C) for some hours in a 1,4-dioxane – hydrochloric acid mixture led to the carboxylic acids **49o, q** and **49p**, respectively (Table 15). These products were first converted by reaction with diphenylphosphoryl azide (DPPA) into the related azides,

Table 17: 4-Arylalkyl- and 4-alkylsubstituted 6-(4-chlorophenyl)-1-methyl-[1,2,4]triazolo[4,3-a][1,3,4]benzotriazepines [31, 32]

Compd.	R
52a	1-naphthyl
52b	2-naphthyl
52c	C ₆ H ₅ CH ₂
52d	C ₆ H ₅ CH ₂ CH ₂
52e	benzhydryl-CH ₂
52f	cyclopropyl
52g	cyclohexyl
52h	cyclohexyl-CH ₂
52i	C ₆ H ₅ –CH=CH
52j	CH ₂ =CH
52k	CH ₂ =C(CH ₃)
52l	CH ₂ =C(Cl)
52m	CH ₂ =C(Br)
52n	CHCl=C(Cl)
52o	CCl ₂ =CH
52p	CF ₃
52q	COOC ₂ H ₅
52r	COOH
52s	C ₂ H ₅ O–CO
52t^a	C ₆ H ₅ –CH(OH)
52u^a	C ₆ H ₅ –CH ₂ CH(OH)
52v	C ₆ H ₅ –CO
52w	C ₆ H ₅ CH ₂ CO
52x^a	(4-Cl–C ₆ H ₄)–CO
52y^a	(4-CH ₃ –C ₆ H ₄)–CO
52z	(2-CH ₃ O–C ₆ H ₄)–CO
53a^a	[2,5-(CH ₃ O) ₂ –C ₆ H ₃]–CO
53b^a	(2-CH ₃ O–C ₆ H ₄)–CH ₂ –CO
53c^a	[2,5-(CH ₃ O) ₂ –C ₆ H ₃]–CH ₂ –CO

Table 18: 4-Carbamoylmethyl-substituted 6-(4-chlorophenyl)-1-methyl-[1,2,4]triazolo[4,3-a][1,3,4]benzotriazepines

Compd.	R	Ref.
54a	propyl	[32]
54b	cyclohexyl	[32]
54c	C ₆ H ₅	[31, 32]
54d	4-CH ₃ –C ₆ H ₄	[31, 32]
54e	2-CH ₃ O–C ₆ H ₄	[31, 32]
54f	2,5-(CH ₃ O) ₂ –C ₆ H ₃	[31, 32]
54g	4-Cl-2,5-(CH ₃ O) ₂ –C ₆ H ₂	[31, 32]
54h	1-naphthyl	[32]
54i	3-pyridyl	[32]

Table 19: 4-Oxyalkyl- and 4-aminoalkyl-substituted 6-(4-chlorophenyl)-1-methyl-[1,2,4]triazolo[4,3-a][1,3,4]benzotriazepines [31, 32]

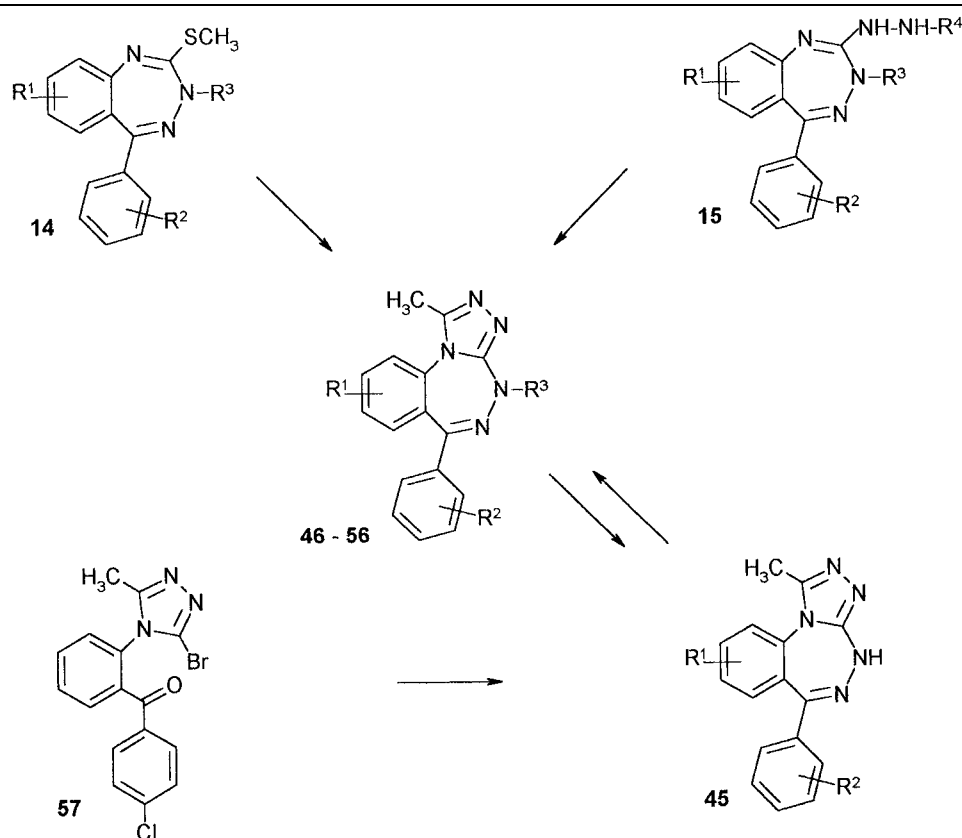
Compd.	n	X	R
55a	1	O	C ₂ H ₅
55b	1	O	4-Cl–C ₆ H ₄
55c	3	O	C ₆ H ₅
55d	1	O	C ₆ H ₅ CH ₂
55e	1	NH	C ₆ H ₅

Table 20: 4-Acyl- and 4-(1-hydroxyalkyl)-substituted 6-(4-chlorophenyl)-1-methyl-[1,2,4]triazolo[4,3-a][1,3,4]benzotriazepines [31, 32]

Compd.	X	R
56a^a	O	BrCH ₂
56b^a	O	(2-CH ₃ O–C ₆ H ₄)–NH–CH ₂
56c	O	C ₆ H ₅ NH–CH ₂
56d^a	O	(4-CH ₃ –C ₆ H ₄)–NH–CH ₂
56e^a	O	(3-F–C ₆ H ₄)–NH–CH ₂
56f^a	O	[2,5-(CH ₃ O) ₂ –C ₆ H ₃]–NH–CH ₂
56g^a	O	C ₆ H ₅ S–CH ₂
56h	O	C ₆ H ₅ CH ₂
56i	O	C ₆ H ₅ –CO
56j	O	C ₆ H ₅ CH ₂ NH
56k	O	(3-CH ₃ –C ₆ H ₄)NH
56l	H, OH	4-CH ₃ SO ₂ –C ₆ H ₄
56m^b	S	C ₆ H ₅ CH ₂

^a ¹H NMR data listed in [31, 32]; ^b in [32] only

Scheme 15

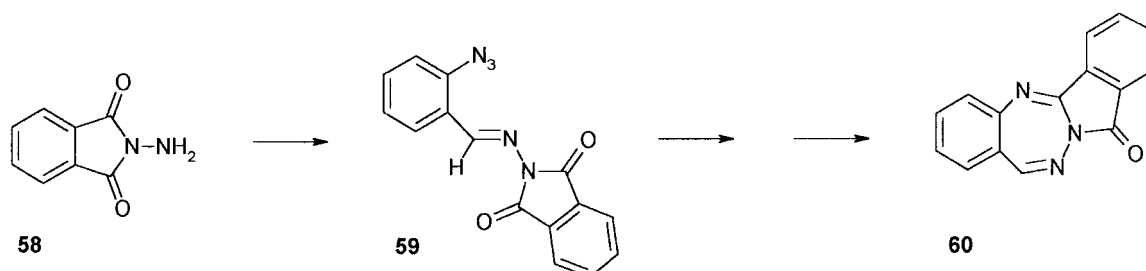


which were made to undergo a Curtius degradation, yielding the carbaminic acid esters **49i–n** (Table 15) in the presence of tertiary butanol. Using a mixture of diluted hydrochloric acid and 1,4-dioxane at room temperature, the hydrolysis of these products provided the hydrochlorides of **49i–k** (Table 15). Oxidation of **49i** with sodium peroxoborate in acetic acid, followed by column chromatographic purification, yielded the 6-(4-nitrophenyl) derivative **49h** (Table 15).

2.2.2. *b*-Anellated 1,3,4-benzotriazepines

Luheshi et al. [33] investigated the formation of related imino phosphoranes from 2-azidobenzoyl and 2-azidobenzylidene derivatives and their intramolecular Aza-Wittig reaction. Thus, **59** was obtained by condensation of 2-azido benzaldehyde with the *N*-amino phthalimide **58**. The transformation of **59** with triethylphosphite (TEP) in toluene provides an insoluble imino phosphorane. The latter cyclized upon heating to give the isoindolo [1,2-*b*][1,3,4]benzotriazepine **60** (Scheme 16); however, no data were given which would confirm the suggested structure.

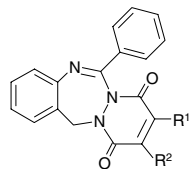
Scheme 16



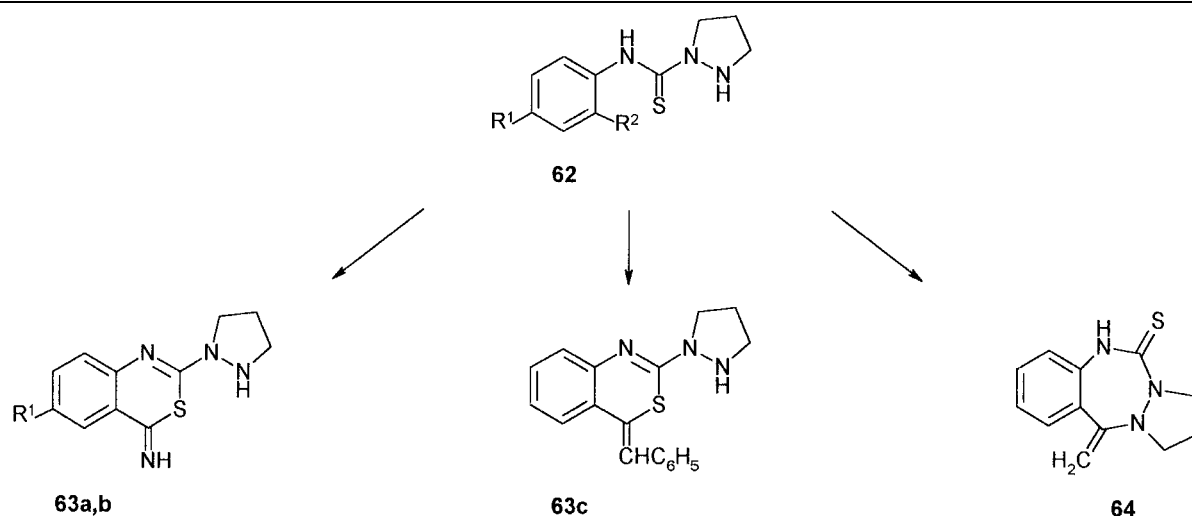
2.2.3. *c*-Anellated 1,3,4-benzotriazepines

c-Anellated 1,3,4-benzotriazepines (Table 21) were reported for the first time by Stankowsky et al. [30]. The compounds **61a, b*** are prepared analogously to **42** by transformation of **43** (see 2.1. and Scheme 13) with the sodium salts of maleic acid hydrazide and phthalic acid hydrazide, respectively. However, no data not even melt-

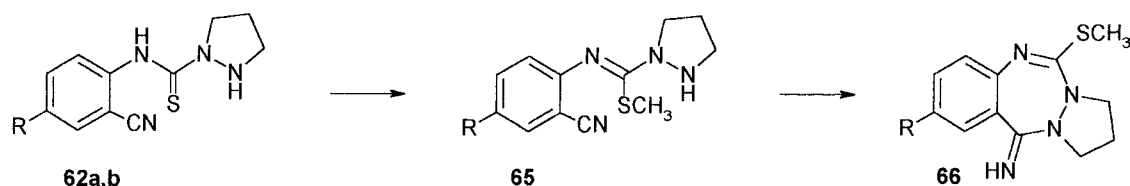
 Table 21: Pyridazino[1,2-*c*]- and phthalazino[2,3-*c*][1,3,4]benzotriazepines [30]

Compd.		
	R ¹	R ²
61a	H	H
61b	–CH=CH–CH=CH–	

Scheme 17



Scheme 18



ings points, are reported that would confirm the structures shown in the publication.

The preparation of pyrazolo[1,2-*c*]- and phthalazino[2,3-*c*]-[1,3,4]benzotriazepines was investigated by Morgenstern et al. [34]. The initial starting material only exceptionally provided the aimed heterosystems. Thus, the intramolecular cyclization of **62a–c** (**62a**: R¹ = H, R² = CN; **62b**: R¹ = Cl, R² = CN; **62c**: R¹ = H, R² = CO–CH₂–C₆H₅) in methanol, which occurs only by aggressive acidic conditions, results in the formation of the 2-pyrazolidino-3,1-benzothiazines **63a–c** (**63a**: R¹ = H; **63b**: R¹ = Cl; as hydrobromides). Starting from the acetophenone **62d** (R¹ = H, R² = CO–CH₃), only the hydrobromide of 11-methylen-5-thioxo-pyrazolo[1,2-*c*][1,3,4]benzotriazepine **64**, the structure of which was confirmed (Scheme 17) by extensive investigations, was obtained.

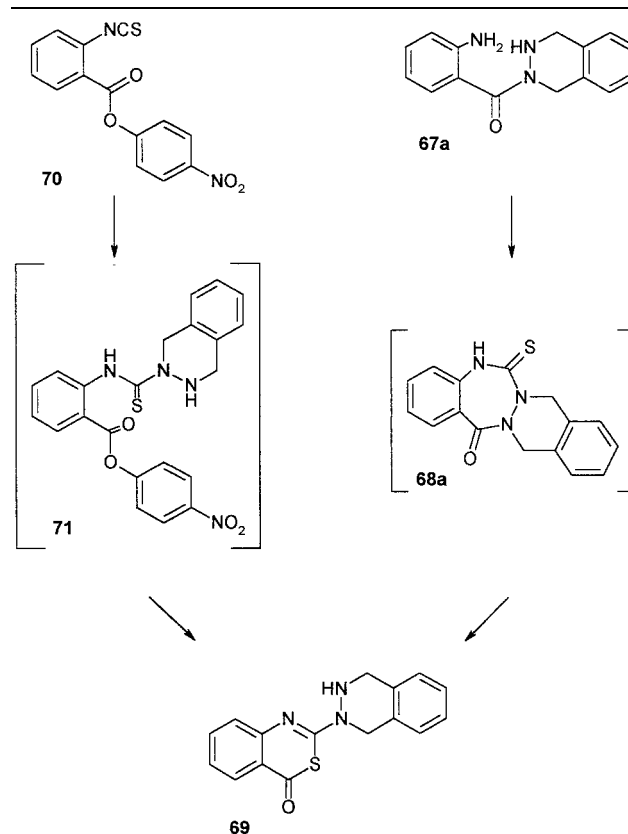
To prevent the formation of ring contracted alternative products, the nucleophilic thio group of **62a, b**, was blocked by methylation. The resulting related methylthio derivative **65** were cyclized in acetone by allowing it to react with hydrobromic acid, yielding the 11-imino heterocycle **66** (Table 22) (Scheme 18). Because these compounds are sensitive to nucleophiles, a successful isolation is only achieved by a quick and careful workup of the reaction mixture.

Table 22: Pyrazolo[1,2-*c*][1,3,4]benzotriazepines [34]

Compd.	R
66a	H
66b	Cl

The same authors investigated the preparation of the phthalazino[2,3-*c*][1,3,4]benzotriazepine **68a** starting from 2-(2-aminobenzoyl)-1,2,3,4-tetrahydropthalazine **67**, which was obtained from isatoic acid anhydride and

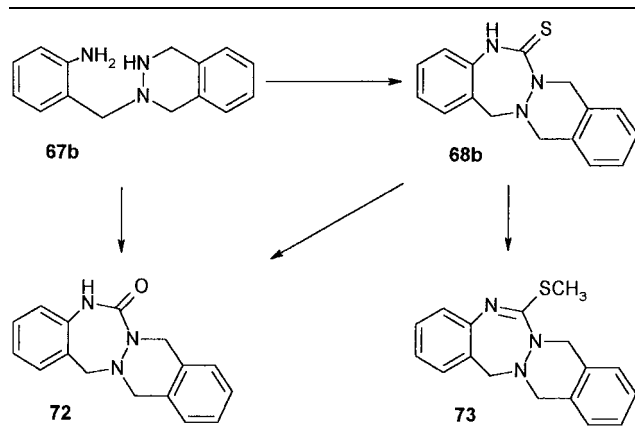
Scheme 19



1,2,3,4-tetrahydrophthalazine hydrochloride. Even under mild conditions, the non-isolable **68a**, which was formed from **67a** and thiophosgene, was quickly transformed into the heterocyclic 2-substituted 3,1-benzothiazin-4-one **69**. The latter was also received when 1,2,3,4-tetrahydrophthalazine reacted with the isothiocyanate **70** at room temperature; the resulting intermediate **71** immediately splits off nitrophenol(ate) (Scheme 19).

That the carbonyl group of **68a** (**67a**) determines significantly the further course of reaction was demonstrated with **67b** (Scheme 20), which was obtained by reduction of 2-(2-nitrobenzyl)-1,2,3,4-tetrahydrophthalazine with tin(II)-chloride. Whereas the reaction with thiophosgene in chloroform resulted in indefinable products, the heterocycle **68b** was formed from the starting compound and a carbon disulfide – triethylamin mixture in refluxing ethanol. In contrast, synthesis of the analogous oxo derivative **72** using chloroformic acid ethyl ester failed. Instead of the desired product, the bis(ethoxycarbonyl) derivative of **67b** was isolated. Nevertheless, the preparation of **72** succeeded by oxidative desulfuration of **68b** in an alkaline hydrogen peroxide solution. The influence of iodomethane on **68b** under mild conditions provided the hydroiodide of **73** in a good yield (Scheme 20).

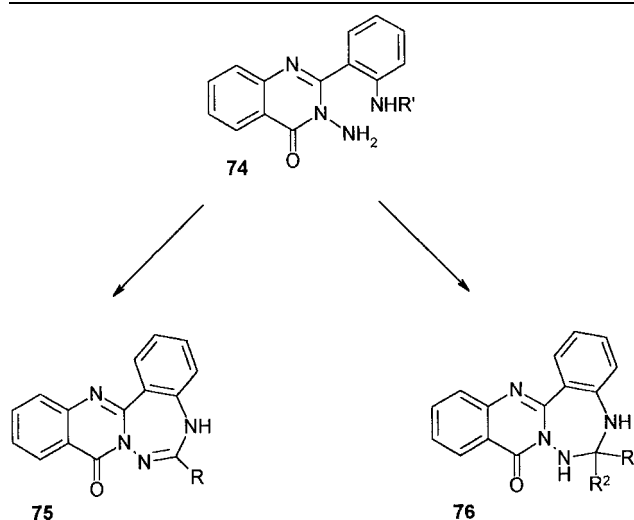
Scheme 20



2.2.4. d-Anellated 1,3,4-benzotriazepines

Novel heterocyclic systems in the form of d-anellated 1,3,4-benzotriazepines were synthesized by Reddy et al. [35] by reaction of 2-(2-aminophenyl)-3-amino-3,4-dihydroquinazolin-4-one **74a** (R' : H) with C_1 -nucleophiles (Scheme 21). The starting compound was synthesized by allowing hydrazine hydrate to react with 2-(2-nitrophenyl)-4H-3,1-benzoxazin-4-one in the presence of Raney nickel (see also [2]). Upon heating **74a** with either orthoformic acid triethyl ester or orthoacetic acid triethyl ester, the quinazolino[3,2-d][1,3,4]benzotriazepines **75a**, **b** (Table 23) were obtained in good yields. In contrast, the analogous reaction with orthopropionic acid triethyl ester only provided the derivative **74b** (R' : COC_2H_5). With carboxylic acids such as acetic acid, aromatic carboxylic acids/PPE, and propionic acid, the products were **74c** (R' : COCH_3), **74d** (R' : COAr), and the N,N' -propionyl derivative of **74a**, respectively. The anellated 1,3,4-benzotriazepines **75c**, **d** (Table 23) were prepared by heating **74a** with phenyl isocyanate and phenyl isothiocyanate, respectively, and likewise gave good yields. Compound **75d** was

Scheme 21


 Table 23: Quinazolino[3,2-d][1,3,4]benzotriazepines **75** [35]

Compd.	R
75a	H
75b	CH_3
75c	SH
75d ^a	OH

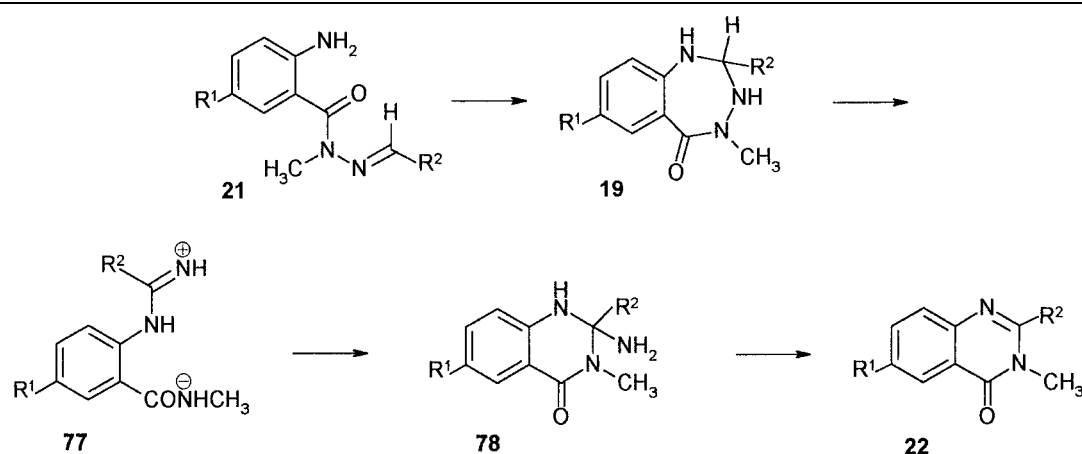
^a predominately existing in the oxo-form

 Table 24: Quinazolino[3,2-d][1,3,4]benzotriazepines **76** [35]

Compd.	R^1	R^2
76a	CH_3	C_2H_5
76b	CH_3	C_3H_7
76c	CH_3	C_6H_5
76d	CH_3	4-Br- C_6H_4
76e		$-(\text{CH}_2)_4-$
76f		$-(\text{CH}_2)_5-$
76g		$-(\text{CH}_2)_6-$
76h		$-(\text{CH}_2)_7-$

synthesized by thermic cyclization of **74e** (R' : COOC_2H_5) at 200 °C. Compound **74e** was formed from **74a** and chloroformic acid ethyl ester in the presence of potassium carbonate. According to the authors, the reaction of **74a** with various ketones gave the heterocycles **76a–h** (Table 24), what is in conformity with the results of the reaction of anthranilic acid hydrazides with carbonyl compounds [11, 12]. The publication cited in [35] on the reaction of aromatic aldehydes with **74a** was already referred in [2] (there ref. [48]).

Scheme 22



2.3. Chemical behavior and structural investigations

The determination of the structure of the compounds **1a–j** (Table 1) obtained by Koldobskii et al. [5–7] is mainly based on the IR spectra, in which absorption bands appear in the range between 3285 cm^{-1} and 3360 cm^{-1} owing to NH valence vibrations. The authors regarded these fact as a sufficient structural confirmation, although in the only ^1H NMR spectrum (of **1a**) of these compounds no NH signal was unambiguously detected, and the data given for the relative molecular mass determined by MS was not comprehensible. But, in accordance with the expectations the hydrolysis of **1a**, which took place in the presence of concentrated hydrochloric acid over 1.5 h, yielded 2-aminobenzophenone (95%) and benzoic acid (63%) [6]. Artamonova and Koldobskii [7] subjected the 2,2'-(1,4-phenylene)bis-(7-methyl-5-phenyl-3H-1,3,4-benzotriazepines) **12a–c** to analogous hydrolysis conditions, and isolated the equimolar amount of terephthalic acid and the two molar amount of the related 2-amino-5-methylbenzophenone. The IR and ^1H NMR data corroborate the structures assigned for **12**.

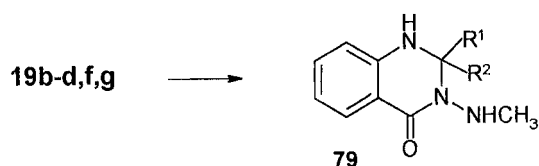
The structural confirmation of the 5-phenyl-1,3,4-benzotriazepines **13–15** is limited to the utilization of the ^1H NMR spectra of selected exponents (see notes in Tables 4–6) [9, 10, 31, 32].

In their studies on the thermic cyclization of the aryliden anthranilic acid hydrazides **21** Shailaja and Reddy [11] isolated the 2-aryl-3-methylquinazolin-4-ones **22** instead of the desired 1,3,4-benzotriazepines (Scheme 5). The authors discussed a reaction course outlined in Scheme 22 [11].

Firstly, the related seven membered heterocycles **19** are formed. By way of the intermediates **77** and **78**, the transformation into the **22** occurs with elimination of ammonia. For structure determination of the benzotriazepines **19** obtained from **20** and *n*-butyraldehyde and ketones, respectively, ^1H NMR spectroscopy (in the case of **19g** also ^{13}C NMR) was used. The recorded spectra were compared with those of the quinazolinones **22**. In particular, the absence of a $\text{CH}=\text{N}$ moiety and the present peaks for 2 NH groups at 4.25–4.60 and 3.65–3.87 ppm are important for the assignments. Furthermore, the peaks representing the molecular ions and intensive peaks due to 2-*N*-alkylidene benzoyl cations in the MS of the compounds support the assigned structure. Moreover, compounds **19b–d, f, g** undergo a ring transformation to the related 3-methylaminoquinazoline derivatives **79** upon heat-

ing for 8 h in ethanolic sodium ethanolate solution. The structure of the **79** was also verified by ^1H NMR spectroscopy [11] (Scheme 23).

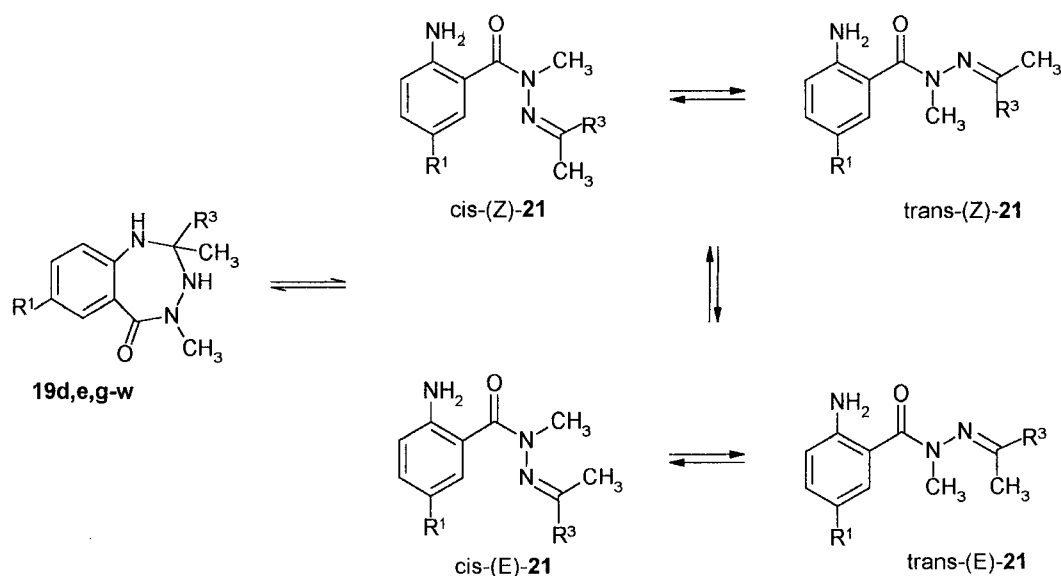
Scheme 23



Pihlaja et al. [12] studied the conformational complexity of the 1,3,4-benzotriazepin-5-ones **19** (Table 7) and their tautomeric ring-chain equilibrium at variable temperatures by one- and two-dimensional NMR spectroscopy. The authors supported their experimental data with molecular-mechanistic and semiempirical molecule orbital calculations, and by x-ray diffractometric investigations [36]. It was found that in various solvents the compounds **19** exist below $-40\text{ }^\circ\text{C}$ completely in the ring-form, whereas at higher temperatures the ring-open form **21** increases as a function of increasing temperature [12, 36]. This ring-open form increases both with the space requirements of the 2-substituents (**19b, g–i**) and with the linking of a chlorine atom in the 7-position (**19o, p**). In place of the 2-arylsubstituted 1,3,4-benzotriazepin-5-ones, **19d** was investigated in detail. It was found that at room temperature the open-chain form is present at a ratio of 50%. As a result of the free rotation of the aryl ring, it gives rise to a high-field shift of the NMR signals of the spatial neighbored substituents by the diamagnetic ring current. Generally, an aryl substituent in the 2-position causes noticeable changes in the thermodynamic behavior; this is explainable by the different electronic and steric properties from these of alkyl groups.

Compounds **19**, which are related to the ring-open compounds **21**, are characterized by peaks at about 165 ppm due to the $\text{C}=\text{N}$ structure in the ^{13}C NMR spectra. In the ^1H and ^{13}C NMR spectra of **19** several sets of signals assigned to the ring-open forms are normally obtained, for which the *trans*- and the *cis*-forms of the related *Z/E*-isomers **21** are discussed (Scheme 24). The rotation of the amide group relative to the aromatic ring is excluded due to a hydrogen bridge existent between the carbonyl and the aromatic amino group. The NMR and x-ray diffracto-

Scheme 24



metric investigations showed that compounds **21** mainly exist in the (*E*)-form. Furthermore, by means of the NOE difference technique, it was verified that the related trans-isomer is favoured (Scheme 24).

According to the authors, the seven membered heterocyclic ring is characterized by a great deal of flexibility and at equilibrium several different conformers exist with the boat-form predominating.

The boat form of **19** exists both in solution at lower temperatures and in the crystalline state. It was found that the C5a, C5, N4, N3, the 5-oxo group, and the carbon atom of the N4-methyl group of **19b** are attached coplanarly, and the C2, together with its substituents, is oriented out of the plane (Fig. 1). Relative to this plane, the benzo-anelland has an angle of about 30°. The lowest-energy process is the pseudorotation of the boat- to the inverse boat-form; several different intermediates are discussed. In this context, the data for the energy barriers of the conformational conversions, which were obtained by NMR spectroscopy, were compared to MMX, MNDO, AM1, and PM3 calculations. In general, all the theoretical methods yielded similar results, but the latter was in the best accordance with the experimental observed facts.

To elucidate the structure of **23**, Reddy et al. [13] gathered the IR, UV, ¹H-, ¹³C NMR and MS of **23a** as well as the chemical behavior of the isolated compounds. Both

the conditions for preparing and also the data listed for this products leaves some doubt about the structures assigned for the **23**. In a previous publication by those investigators [37] (see also [2]), incorrect assignments were made to the structures of compounds originally thought to be 1,3,4-benzotriazepin-5-ones; this interpretation was corrected some time later by Fülöp et al. [38]. They showed that the reaction of anthranilic acid hydrazide with benzylidene anilines does not result in the postulated compounds, but in the benzylidene anthranilic acid hydrazides.

The compounds described as **23** [13] undergo both a ring transformation to **80** by reaction of sodium hydroxide and a desulfuration, providing **81** in the presence of Raney nickel in methanol and a hydrogen peroxide-acetic acid mixture, respectively.

Regarding the structure elucidation of the 4-*tert*-butyl-1,3,4-benzotriazepin-2,4-dione **33a** synthesized by Karp [23], the compound was thionated with Lawesson's reagent. The 2-thioxo analogue **33b**, which is also formed by the reaction of **31d** with thiophosgene, was isolated in a good yield. Furthermore, the author studied the alkylation of **33** with sodium hydride/iodoalkanes. Whereas the

Scheme 25

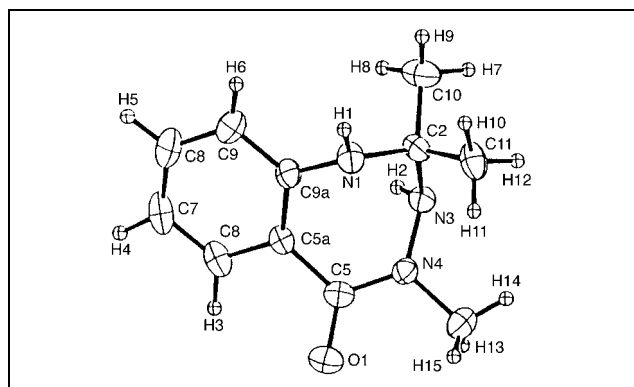
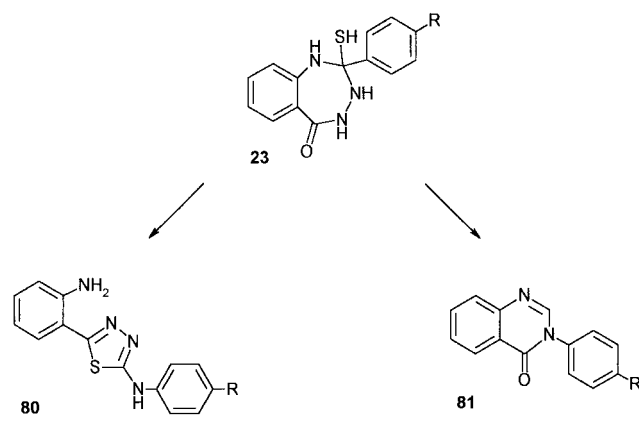

 Fig. 1: Molecular structure of **19b** in crystalline state (ORTEP) [36]

Table 25: Selected ^1H and ^{13}C NMR data of 4-*tert.* butyl-5-oxo-1,3,4-benzotriazepines **33** and **36** (chemical shifts δ in ppm) [23]

33		36	

Compd.	X	R	N1-H	N3-H	N3-CH ₃	S-CH ₃	C2	C5
33a	O	H	9,49	8,81	—	—	164,3	166,9
33b	S	H	10,85	10,00	—	—	193,1	166,9
33c	O	CH ₃	9,46	—	3,06	—	163,8	167,4
36	—	—	9,25	—	—	2,43	160,8	163,6

2-thioxo-1,3,4-benzotriazepine **33b** is S-alkylated to give **36**, **33a** provides the 3-alkyl derivatives **33c, d** (Scheme 10). All the recorded ^1H and ^{13}C NMR as well as mass spectrometric data of these products are in agreement with the assigned structures (Table 25). To identify the site of alkylation at **33**, the 1D-NOE difference spectra and proton-carbon correlation spectra (with and without deuterium exchange) were used.

Initial evidence for the formation of the 4-phenyl-1,3,4-benzotriazepine **40a** (Table 11) through the reaction of formaldehyde with 2-oxoadipic acid 6-methylester N^1, N^3 -diphenyl-amidrazone instead an aimed Δ^2 -1,2,4-triazoline came from the IR spectrum of the isolated compound [28]. Unexpectedly, an intensive NH valence peak was observed in the spectrum. By means of further ^1H and ^{13}C NMR spectroscopy it was shown, that ring closure does not occur between the N1 and the N3 of the amidrazone structure but rather between N1 and the 2-position of the phenyl ring attached at the N3-position. This finding was corroborated by the attached-proton-transfer carbon spectrum, in which one signal in the range of the aromatic carbon atoms could not be correlated with an aromatic CH group. Similarly, the structure of the other, yellow coloured **40** was also confirmed. With the exception of **40f**, the molecular ion peak represents the basis peak in the electron-impact (70 eV) mass spectra of the **40**. The x-ray structural analysis of **40a** [28, 29] provides evidence for the structure assigned to **40**. Formation of the bis[4-(1,3,4-benzotriazepin-4-yl)-phenyl]methane derivative **41** was concluded from the comparison of the ^1H NMR spectrum with that of **40a** (additional signal due to the linking methylen group at 3.91 ppm) as well as from the MS (molecular ion peak at m/z 714). The confirmation of the structure of the a-anellated 1,3,4-benzotriazepines **45** (Table 13), **46–48** (Table 14) **49, 50** (Table 15), **51** (Table 16) **52, 53** (Table 17), **54** (Table 18), **55** (Table 19) and **56** (Table 20) reported in the patent literature [31, 32] is restricted to ^1H NMR of selected compounds (see notes in the Tables).

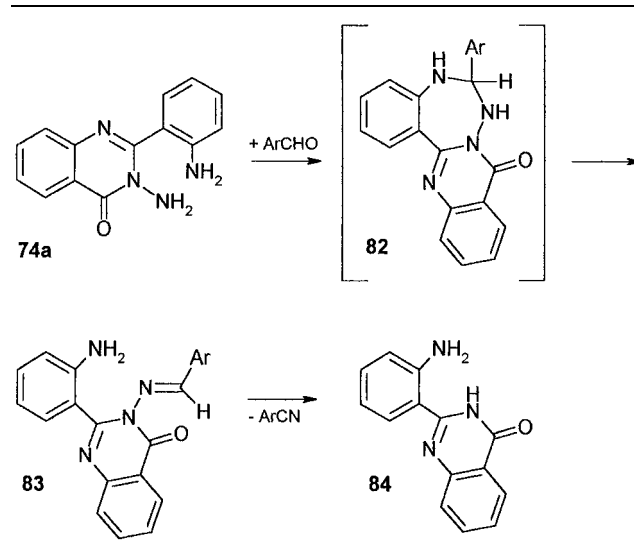
Morgenstern et al. [34] confirmed the structures of the isolated seven membered heterocycles **68b**, **72**, and **73** (Scheme 20) by means of UV, IR, ^1H , ^{13}C NMR, and EI-MS. Thus, the IR spectrum of **68b** does not provide evidence for ring-contracted products, and the MS shows an intensive $[\text{M}-33 (\text{SH})]^+$ -peak, indicating a clear relationship to the 5-phenyl-2-thioxo-1,3,4-benzotriazepines [2] (there ref. [66]). Moreover, ^1H and ^{13}C NMR spectra ($\text{DMSO}-d_6$) of these compound are in accordance with the assigned structure. The signals appear for the proton of

the $\text{NH}-\text{C}=\text{S}$ structure and for the thiocarbonyl-carbon at $\delta = 10,09$ ppm and $\delta = 180,17$ ppm, respectively, and are comparable with those of the related compounds [2, 23]. By comparison of the IR spectra of **72** and **73**, the absorption at 1188 cm^{-1} was assigned to the thiocarbonyl group. In addition, the spectral data of **72**, obtained by oxidative desulfuration of **68b**, argue against both a ring-open and a ring-contracted alternative structure. To identify the site of alkylation of **68b** and to prove the formation of the S-methyl derivatives **73**, the spectra of these compounds as well as studies on the exchange of the sulfur for nucleophiles were used. Because of the clearly different UV spectra and the missing of a signal due to the thiocarbonyl group in the ^{13}C NMR spectrum of **73**, the N-methylation was excluded. Additionally, there is a peak due to a $[\text{M}-47 (\text{CH}_3\text{S})]^+$ -ion in the MS. Furthermore, the influence of amines on **73** causes the generation of methanethiol.

To determine the structure of 11-methylen-5-thioxo-pyrazolo[1,2-*c*][1,3,4]benzotriazepine **64** obtained from **62d**, the ^1H and ^{13}C NMR spectra as well as UV and MS of the 3,1-benzothiazines **63** were used for comparative studies. In particular, both the presence of characteristic NMR peaks due to the $\text{NH}-\text{C}=\text{S}$ structure (NH : 12,43 ppm; $\text{C}=\text{S}$: 193,06 ppm; in $\text{DMSO}-d_6$), which do not appear in the related spectra of **63**, and the mass spectrometric behavior [intensive molecular ion peak representing the basis peak and absence of $[\text{M}^{++}-72]$ -peaks (splitting off of pyrazolidine; typically for **63**; basis peak in the MS of **63a**)] corroborate the structure assigned to **64**. Moreover, the UV spectra of **63** and **64** differ considerably.

As arguments in favour of the structures assigned to the **75** (Scheme 21, Table 23) obtained by Reddy et al. [35] the authors listed the spectral data of these compounds without discussion. In the case of **76** (Table 24), it was mentioned that the UV, IR, and MS (no data) are consistent with the suggested structures; however, only limited data are given for **76b**. In order to assign the structure, the authors laid particular importance on the singulets at 2,83 ppm (low-field shifted methyl group), at 8,80 ppm (deuterium exchangeable NH), and at 9,64 ppm (deuterium exchangeable NH) in the ^1H NMR spectrum (CDCl_3), and the two separate NH peaks exclude an alternative ring-open azomethine structure. Furthermore, they also

Scheme 26



made the stability of the compounds an additional argument for the quinazolino[3,2-*d*][1,3,4]benzotriazepine structure of **76**. In the same publication, the reactivity of the products obtained from **74a** and benzaldehydes is reported. Because of the absence of the azomethine proton in the ^1H NMR spectrum, these compounds were described as 6-aryl-9-oxo-chinazolino[3,2-*d*][1,3,4]benzotriazepines **82***. Upon heating **82** in diphenyl ether in the presence of palladium-activated coal, to the opinion of the authors a decomposition of the seven membered heterocycle occurs via **83**, and the 2-(2-aminophenyl)-quinazolin-4-one **84** as well as the related aryl cyanides (verification by TLC) are formed (Scheme 26).

3. Biological activity

3.1. 5-Aryl substituted 1,3,4-benzotriazepines

As analogues of peripherally acting benzodiazepines, the 2-oxo-5-phenyl derivatives **13b–h** (Table 4) and the pharmaceutically relevant salts were claimed in a patent [9]. In relation to diazepam and clonazepam, the compounds show an extremely high selectivity to peripheral benzodiazepine receptors, which have been found at higher levels in various tumor tissues (lung, breast, prostate, pancreas). The competitive occupation of these receptors by these compounds *in vitro* results in suppression of the tumor proliferation via an unknown mechanism. The compounds are to be used in cancer therapy both directly and as selective carriers for cytotoxic agents, such as α -radiation emitting radioisotopes, ricine, and diphtheria toxine. The two derivatives **13m, n** mentioned in the patent [10] are among a number of benzo- and thieno-condensed derivatives of various diazepines, oxazepines, thiazepines, and of azepine. These compounds are inhibitors of the human squalene synthetase and may be useful as drugs for the treatment of hypercholesterinemia and arteriosclerosis. Of importance is the fact that the farnesyl pyrophosphatase and therefore the synthesis of ubiquinone, dolichole, and heme A is not interfered upon. No detailed information on the biological activity are given for the 1,3,4-benzotriazepine derivatives **13m, n** in the patent.

3.2. 1,3,4-Benzotriazepin-5-ones

The ring-contracted compounds **32** (Scheme 9), which erroneously were reported by Nawrocka et al. [19] to be the 2-thioxo-1,3,4-benzotriazepines **30a, b**, show anxiolytic (**32a**) and analgesic (**32b**) activities.

Relating to the structure-activity studies of herbicidal 1,4-benzodiazepin-2,5-diones Karp et al. [24] also varied the seven membered heterocyclic ring, and compounds **33** (Scheme 10) were obtained. Whereas many of the 1,4-benzodiazepin-2,5-diones that were studied are active against broadleaf weeds, **33a, c, d** were inactive even at the highest rates tested.

The 1,3,4-benzotriazepin-5-ones **37** and **38** (Tables 9 and 10), and the pharmaceutically relevant salts, which were claimed in [24], were found to be calcium antagonists and potassium channel activators. The relatively nontoxic compounds diminish considerably the repolarization time of the action potential of isolated Purkinje fiber specimen (dog) (data listed for **38c, i, m, n, p, r**), and inhibit remarkably the increase of the vasopressin-induced elevation of the ECG ST segment (CFY-rat) (data listed for **38m, n, p, r**). Compounds **37** and **38** should be useful as remedies for Angina pectoris and hypertension.

3.3. Anellated 1,3,4-benzotriazepines

As potential drugs for the treatment of osteoporosis, hypercalcemia, Paget's disease (Ostitis deformans), and rheumatoid arthritis the relatively nontoxic a-anellated 1,3,4-benzotriazepines **45–56** (tables 13–20) and their pharmaceutically relevant salts were claimed in the patent literature [31]. The studied compounds inhibit the calcium release from new born ICR mouse calvaria bone *in vitro*; and **45g** and **47h** were the most active (determination of released ^{45}Ca ; data listed for **45g, 46a–d, f–h, j, n, o, q, s, v, w, y, 47g, h, m–o, s, v, x–z, 48a–c, 49d, 51a, b, d, e, h, n, p, r, t, v, 52f, h, k–m**). *In vivo* (ovariectomized, osteoporosis model rat) the compounds caused a suppression of the bone mass decrease depending on dosage upon orally application for 12 weeks (measuring of the bone mineral density of lumbar spine (L 4–5); data listed for **51d, v**).

The same compounds are also reported to inhibit markedly the cytokine production [32]. Thus, *in vitro* the lipopolysaccharide-induced production of interleukine 6 and 8, tumor necrosis faktor α as well as GMCSF (human PBM cells; data listed for **46w, z, 47h, 49a, e, g, i, j, k, u, 50a, b, 51b, d, e, f, p, r, t, v**), and the formation of interleukine 2 and interferone- γ induced by concanavaline A is decreased (balb/c-mice spleen cells; data listed for **51d**). *In vivo* (Lewis rats) the compounds show a significant activity against arthritis induced by *Mycobacterium butyricum* (suppression of edema of hind limb; data listed for **51d**). The a-anellated 1,3,4-benzotriazepines tested represent potential drugs for prophylaxis and therapy of diseases in which cytokines play an important role. Among these are various chronic inflammations, autoimmune, cancer, and virus diseases.

¹ Part 1: Pharmazie **39**, 301 (1984); part 2: Pharmazie **47**, 655 (1992)

² Parts 1 and 2 are the basis for a review of Russian authors [3, 4].

³ In the Tables are only listed such compounds which are not referred to earlier [1, 2].

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