Bis(1,3,4-thiadiazolo)-1,3,5-triazinium Halides. 2.† Intramolecular Ring Transformation and Synthesis of Novel Highly Substituted Guanidines‖

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Bis(1,3,4-thiadiazolo)-1,3,5-triazinium halides **6** can be easily attacked by nucleophiles at either the C(3a) or the C(4a) position of the central six-membered (cationic) ring. Nucleophilic attack leads to at least two reaction channels, one of which has been previously detected (pathway a) and leads to novel aminals **19**. In this paper we report on a second channel (pathway b). Attack of primary or secondary amines **8** at C(3a) or C(4a) in **6** (and their analogues **7**) leads to the weakly stabilized intermediates **14**. A cascade of several proton shifts, ring openings, rearrangements, and ring closure processes is initiated which finally leads via **17** and **18** to novel highly substituted guanidines **9**, **10**, **12**, and **13**. Pathway b seems to be the result of well-balanced negative-hyperconjugative effects in **14** and/or **17** which control the highly selective opening of a relatively stable central 1,3,5-triazinium ring to yield the crucial intermediate **18**. Some representatives of the guanidines have been characterized by X-ray analyses. Since some of the guanidines contain one or two chirality centers, an effort was made to investigate the stereochemistry of these compounds.

Introduction

In the course of a three-component reaction of an aldehyde **1**, a thionyl halide **2** and a variety of hetarenes (pyridine and pyridine derivatives, methylimidazole, quinolines etc.), *N*-(1-haloalkyl)pyridinium halides **3**[1,2] are readily accessible. As recently reported, these salts **3** react with 2-amino-1,3,4-thiadiazoles **4** to yield the novel cationic 5/6/5-heterocycles, the bis(1,3,4-thiadiazolo)-1,3,5-triazinium halides **6**[1,3] (Scheme 1). The products **6** are generated with almost 80% yields in the course of a multistep cascade reaction of **3** with the heterocycles **4**. The 5/6/5-heterocycles **6** can be transformed into novel bis(thiadiazolyl)alkanes ("aminals", Scheme 5)[3] by employing an excess of **4** and slightly varying the reaction conditions. This reaction indicates that both centers C(3a) and C(4a) (Scheme 1) are suitable for nucleophilic reactions which, in the case of **4a**, yields the aminals via another multistep reaction under extrusion of pyridine and the corresponding ammonium halide. This assumption is supported by calculating the charges at these centers. Both ab initio and DFT-methods[4−6] predict these centers to be significantly positively charged (results of natural population analyses[7] for the model cation of **6**: $R^1 = CH_3$, $R^2 = H$; $q_{C3a} = q_{C4a} = +0.40$ e; HF/6-31G* opt. +0.25 e; B3LYP/6-31G* opt.). All previously performed as well as our ongoing studies demonstrate that the instability of the initial intermediates **14** (Scheme 5) should—depending on the properties of the incoming nucleophile **8**—open surprising reaction channels in addition to the "5/6/5 to aminal" transformation. We report here on experimental investigations which support this assumption since we succeeded in finding a novel procedure for the preparation of highly substituted guanidines **9**, **10**, **12**, and **13** (Schemes 2−4).

All of the intermediate ring opening/ring closure reactions are determined by the influence of well-balanced stereoelectronic effects. Furthermore, reaction pathway b for compounds **6** (or the benzofused derivatives **7**) with aliphatic amines are the first examples of a novel heterocyclic ring transformation via an unexpected rearrangement process.

Guanidines represent one of the most extensively investigated class of carbonic acid derivatives.[8] The

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‖ Dedicated to Professor Ernst-Gottfried Jäger (Jena, Germany) on the occasion of his 65th birthday.

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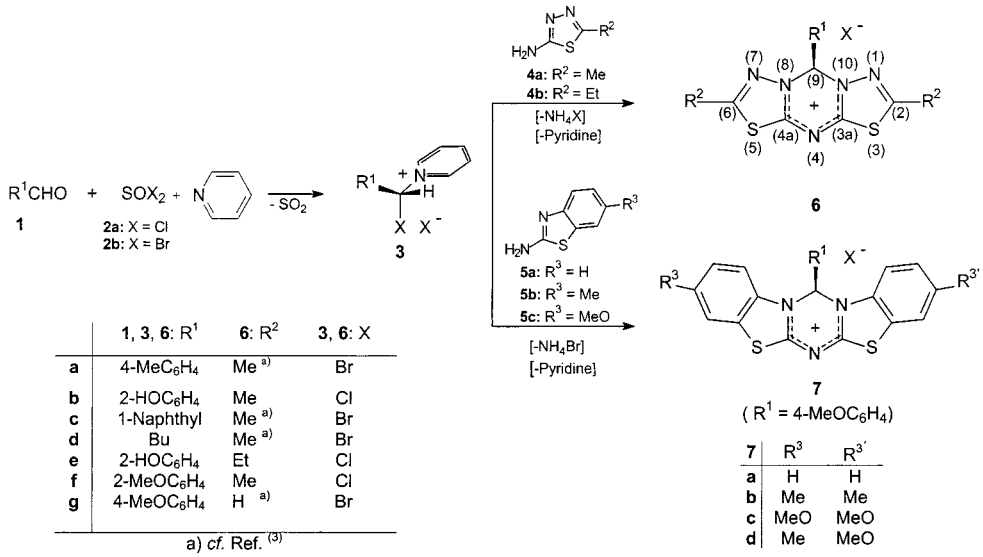
Scheme 1. "5/6/5" Halogenides 6 and 7 from *N*-(1-Haloalkyl)pyridinium Salts 3 and Heterocyclic Compounds 4 and 5



	1, 3, 6: R^1	6: R^2	3, 6: X
a	4-MeC_6H_4	Me [a]	Br
b	2-HOC_6H_4	Me	Cl
c	1-Naphthyl	Me [a]	Br
d	Bu	Me [a]	Br
e	2-HOC_6H_4	Et	Cl
f	2-$MeOC_6H_4$	Me	Cl
g	4-$MeOC_6H_4$	H [a]	Br

a) *cf.* Ref. [3]

7	R^3	$R^{3'}$
a	H	H
b	Me	Me
c	MeO	MeO
d	Me	MeO

various synthetic procedures which yield such compounds employ amines and various carbonic acid derivatives as reactants.[9] However, only a few guanidines, in which **A**, **B**, and **C** represent nitrogen heterocycles, have been reported (Figure 1). Such compounds were prepared, for example, from appropriate dithiocarbonimidates and corresponding heterocyclic amines,[10] or from halo substituted heterocycles and guanidines, or from amino heterocycles and isothioureas.[11]

Results and Discussion

Starting from *N*-(1-haloalkyl)pyridinium halides **3** and aminothiadiazoles **4**, the bis[1,3,4-]thiadiazolo[3,2-*a*: 3′,2′-*d*]-[1,3,5]-triazin-8-ium halides **6** were synthesized[1,3] (Scheme 1). Salts **3** were prepared from a 1:1:1 molar ratio of reactants **1**, **2**, and pyridine. For the synthesis of **3b** (which has not yet been described in the literature), the presence of 2 equivof **2a** is required due to the presence of an reactive OH group in the aldehyde component. The regeneration of the OH function was performed by methanolysis. The molecular structure of **3b** was studied by X-ray analysis,[12] it is structurally quite similar to the corresponding methoxy derivative **3f**[13] when one compares the most important bond lengths and bond angles. The 5/6/5 heterocycles **6b**, **e**, and **f** were obtained in yields up to 82% by procedures analogous to those described previously for **6a**, **c**, **d,** and **g**.[3] The novel bis-benzothiazolo-1,3,5-triazinium bromides **7a**−**d** were

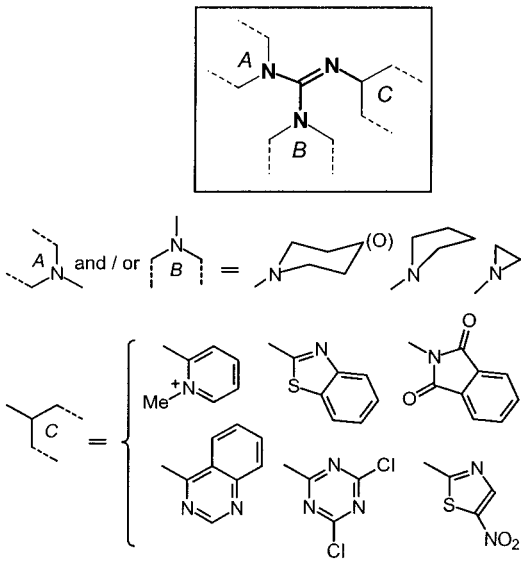


Figure 1. Heterocyclic moieties of previously prepared guanidines, cf. refs 10, 11.

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(12) Crystallographic data (excluding structure factors) for the structures **3b**, **9a**, **9n**, and **12a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 146230 (**3b**), 146150 (**9a**), 146149 (**9n**), 146151 (**12a**, racem.), 146152 (**12a**, meso). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (Fax: (+44)1223-336-033; E-mail: deposite@ccdc.cam.ac.uk).

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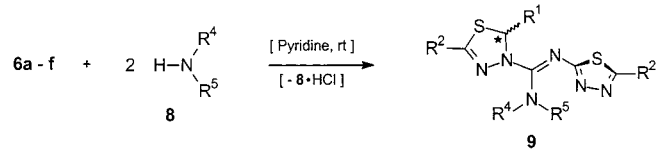
Scheme 2. Guanidines 9 from the Thiadiazolo "5/6/5" Salts 6 and Primary and Secondary Amines 8

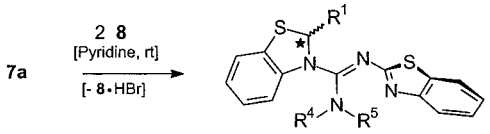


8	R^4 / R^5
a	-$(CH_2)_5$- [a]
b	-$(CH2)_2$-O-$(CH_2)_2$- [b]
c	-$(CH_2)_4$- [c]
d	-Et, -Et
e	-H, -Bu
f	-H, -$(CH_2)_2$-2-Py [d]

a) Piperidino
b) Morpholino
c) Pyrrolidino
d) 2-(2-Pyridyl)-ethylamino

9	R^1	R^2	R^4 / R^5: *cf.* Compounds **8**
a	4-MeC_6H_4	Me	a
b	4-MeC_6H_4	Me	b
c	4-MeC_6H_4	Me	c
d	4-MeC_6H_4	Me	d
e	2-HOC_6H_4	Me	e
f	2-HOC_6H_4	Me	b
g	1-Naphthyl	Me	a
h	1-Naphthyl	Me	b
i	Bu	Me	a
j	Bu	Me	b
k	2-HOC_6H_4	Et	c
l	2-HOC_6H_4	Et	b
m	4-MeC_6H_4	Me	e
n	1-Naphthyl	Me	e
o	Bu	Me	e
p	2-HOC_6H_4	Et	f

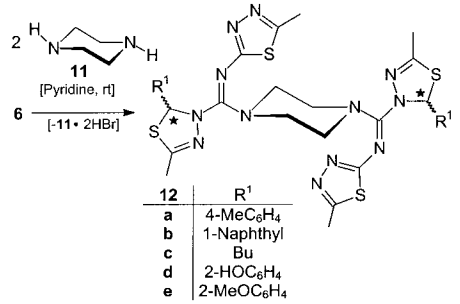
Scheme 3. Benzo-Fused Examples: Guanidines 10 from the Benzothiazolo "5/6/5" Salt 7a and Primary and Secondary Amines 8



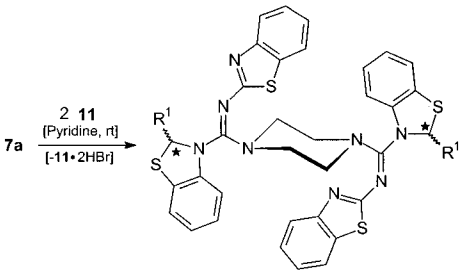
10 [a]	R^4 / R^5: *cf.* Compounds **8**
a	a
b	b
c	c
d	f

a) R^1 = 4-$MeOC_6H_4$

Scheme 4 Bis-guanidines (12, 13) from 6 or 7a and Piperazine



12	R^1
a	4-MeC_6H_4
b	1-Naphthyl
c	Bu
d	2-HOC_6H_4
e	2-$MeOC_6H_4$



13 (R^1 = 4-$MeOC_6H_4$)

analogously synthesized by the cyclization reaction of 1,1′-[(4-methoxyphenyl)methylene]-bis-pyridinium dibromide[3] with 2-aminobenzothiazoles **5a**−**c** (ca. 40% yield) and were characterized by NMR, MS, UV spectra, and elemental analyses. The potential of our 5/6/5 heterocycle synthesis is, thus, not restricted to the sole use of aminothiadiazoles **4**. Interestingly enough, these compounds **7** possess intensive fluorescence properties.

Whereas the reaction of **6** with an amine **4** yields the compound **19** (pathway a, Scheme 5), a complete different reaction pathway b for **6** (and **7**) was observed after exchanging **4** for primary and secondary amines **8** or **11**. The novel guanidines **9** (from **6a**−**f**, Scheme 2), **10** (from **7a**, Scheme 3), **12** (from **6a**−**e**, Scheme 4), and **13** (from **7a**, Scheme 4), could be obtained with very good yields. The best results (**9a**−**p**, **10a**−**d**, **12a**−**e**, and **13**: 80−90%) are obtained in pyridine solution at room temperature and employing 2 equiv of the amines **8a**−**f**.[14] The excess of amine is required to bind the HX formed in the course of the reaction.

Structural Assignments. Structural assignments of the guanidines **9**, **10**, **12**, and **13** were based on NMR data, mass spectra (CI), IR spectra (ATR), and elemental analyses. As already mentioned, the cyclic carbon atom (C(3a) or C(4a)) that undergoes nucleophilic attack is transformed in the course of the reaction into the exocyclic C(1) of the guanidine unit. This transformation causes a shift in the ^{13}C signals toward higher fields (ca. 15 ppm) as compared with the parent compounds **6** and **7**. The reaction causes a similar shift toward higher fields for the HC(9) and C(9) ($^1H \approx 1$ ppm; $^{13}C \approx 7$ ppm) since C(9) in the cationic system has been converted into the C(2) atom of the new dihydrothiadiazole ring. All of the ^1H and ^{13}C NMR signals of the rearrangement products have been unambiguously assigned to the dihydrothiadiazole, the aromatic thiadiazole ring, and guanidine unit via HMQC, HMBC, COSY, TOCSY, and NOESY correlations. These spectra are in agreement with the postulated structures (cf. Supporting Information). Noteworthy is an NOE experiment on compound **9a** which shows a correlation between the HC(2) signal of the dihydrothiadiazole ring ($\delta = 6.91$) and the HC(2′) (or HC(6′)) protons of the piperidyl moiety ($\delta = 3.02/3.23$). In addition, a correlation is observed between the HC(2″)/HC(6″) pro-

(14) The reaction can be also proceed with one equivalent amine and triethylamine as solvent.

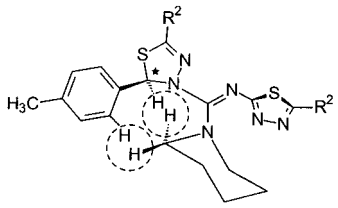


Figure 2. NOE correlations in the guanidine **9a**.

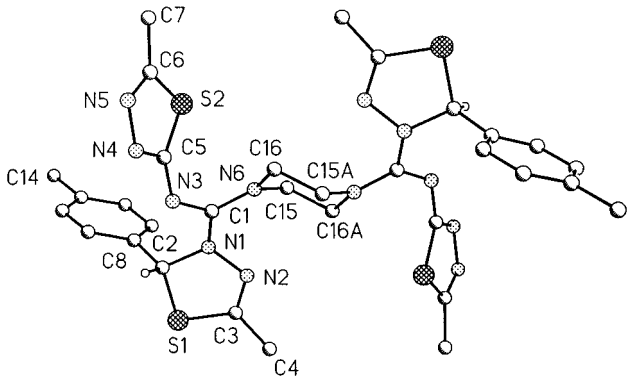


Figure 3. Crystal structure of the (*R*,*S*) meso isomer of **12a**, a representative of the novel guanidines. For further crystal structures cf. Supporting Information. Selected bond lengths [pm] and bond angles [deg]: C(1)−N(1) 138.6(3), C(1)−N(3) 130.6(3), C(1)−N(6) 136.7(3), C(2)−N(1) 149.1(3), C(2)−S(1) 183.8(3), C(5)−N(3) 137.3(3), C(5)−S(2) 176.0(3), C(3)−N(2) 128.5(3); N(1)−C(1)−N(3) 116.1(2), N(1)−C(1)−N(6) 116.8(2), N(3)−C(1)−N(6) 127.1(2), N(1)−C(2)−H(2) 108.7(18), C(8)−C(2)−H(2) 109.7(18), N(1)−C(2)−S(1) 102.56(18), C(8)−C(2)−S(1) 112.26(19), N(1)−C(2)−C(8) 113.4(2), S(1)−C(2)−H(2) 110.0(18).

tons of the phenyl group (δ = 7.18 ppm) with the same piperidyl protons (Figure 2).

These findings indicate that, in solution, the NR^4R^5 moiety (cf. Scheme 2) of the original nucleophile and the substituent at C(2) of the newly generated dihydrothiadiazole ring can approach each other due to relatively unhindered rotations around the corresponding C−N bonds. Steric effects apparently do not play an important role.

The structures of compounds **9a**, **9n**, and **12a** (racemic mixtures and the meso compound) were confirmed by X-ray analyses (Figure 3, vide infra, and Figures 5 − 7, cf. Supporting Information). The arrangement of the aromatic thiadiazole and the dihydrothiadiazole ring shows the expected *E*-stereochemistry at the imine double bond. Important bond lengths and bond angles are in agreement with the expected properties of a guanidine unit which has been substituted by moieties stemming from the nucleophiles **8** and **11**. These data show the existence of an unconjugated (shorter) C = N bond (≈128 pm) and a somewhat longer C=N bond (≈131 pm) which conjugates with the heteroaromatic ring C=N bonds. This corresponds, for example, with the IR spectrum of **9a** which shows a sharp absorption signal (1573 cm^{-1}) due to the guanidine C=N bond and a weaker absorption peak (1614 cm^{-1}) due to the isolated dihydrothiadiazole C=N bond. Significant differences in bond lengths and angles are not observed in the guanidine structure moieties of **9a**, **9n**, and **12a**. The racemic **12a** (Figure 7, cf. Supporting Information) possesses C_{2v} symmetry in the solid state. This contrasts with the

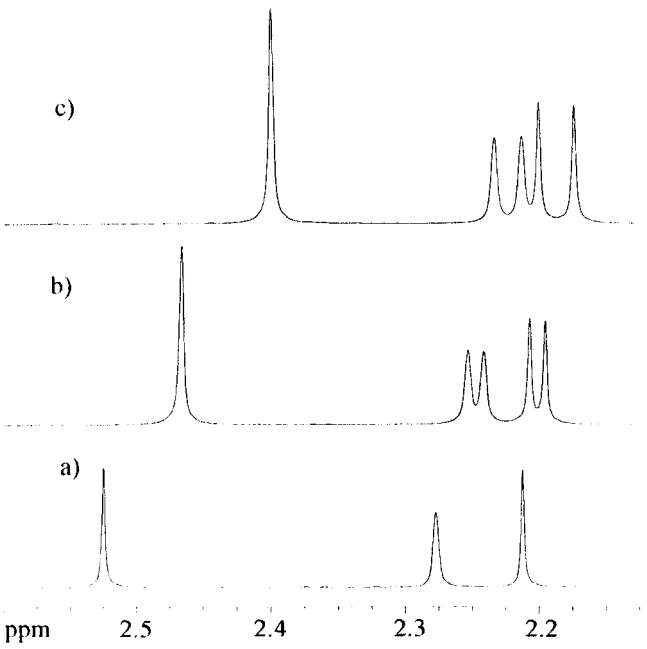


Figure 4. ^{1}H NMR investigation of **9a** (racemate; 30 mg, 0.074 mmol, in $CDCl_3$); shift reagent: (*S*)-(+)2,2,2-trifluoro-1-(9-anthryl)ethanol. (a) without shift reagent; (b) addition of 0.036 mmol; (c) addition of (total) 0.072 mmol.

achiral diastereomer (the meso isomer, Figure 3) which possesses an inversion center.

Furthermore, it is noteworthy that this rearrangement gives rise to a new chiral center at the 2,3-dihydrothiadiazole ring. As expected, the products **9** and **10** were obtained as racemic mixtures. This was confirmed by the analysis of the ^{1}H NMR spectra of **9a** obtained in the presence of the shift reagent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.[15] For example, the Me signals both of the dihydrothiadiazole unit at 2.21 and the 4-tolyl Me at 2.27, and the Me group of the aromatic thiadiazole ring at 2.53 ppm, show a significant shift toward higher fields after addition of the above-mentioned reagent (Figure 4). If R^1 is a butyl group (**9i**, **9j**, **9o**), the protons in the methylene group in the neighborhood of the new chiral center are diastereotopic. Compounds **12** and **13** contain two chiral centers. In the case of **12a**, the corresponding racemic mixture and the meso structures could be easily isolated by crystallization from MeOH.

Some Mechanistic Considerations. The overall results of these reactions can be summarized as follows: The attack of amine nitrogen occurs, as expected, at the electrophilic carbon atom C(3a) or C(4a) which initiates an unexpected reaction cascade. The most important steps are the cleavage of *both* the S(5)−C(4a) bond in the thiadiazole and of the C(9)−N(10) bond in the triazinium ring. This initiates an interesting rearrangement. The sp^3-C(9) atom in the triazinium system becomes a sp^3-center in the newly formed 2,3-dihydro-thiadiazole ring in the course of the cascade whereas C(9)−N(10) bond cleavage leads to the final guanidine moiety (Schemes 2−4). The C(4a) ring atom of the 5/6/5 cation becomes the central guanidine C atom which also bears the NR^4R^5 moiety of the (former) nucleophilic primary and or secondary amine component. This rearrangement process

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completely destroys the central 1,3,5-triazinium ring of **6** and **7**.

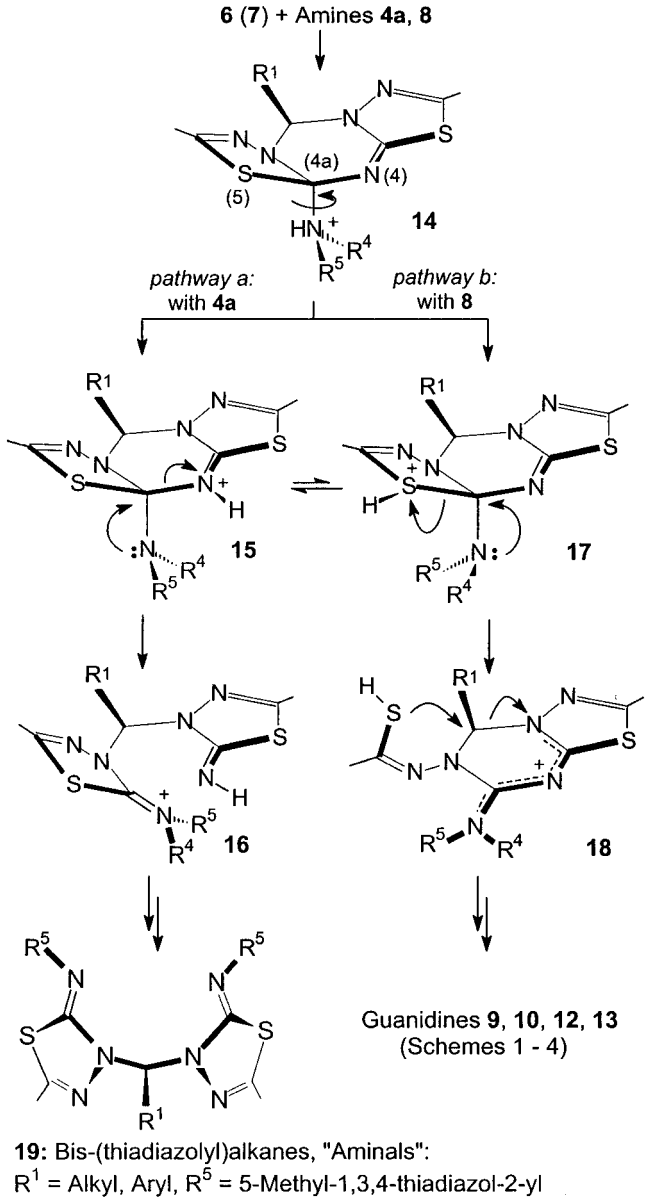
It is difficult to find at least slightly analogous rearrangement reactions in the literature.[16−20] For example, our results cannot be directly compared with either the classical Dimroth-[16] or with the related Angeli-rearrangement[21] or with other so-called "ring-degenerate rearrangements" of heterocylic systems.[18]

On the basis of initial calculations (vide supra) and the knowledge of the final structures (compounds **9**, **10**, **12** and **13**), the key step in the reaction sequence is most probably an equilibrium reaction resulting from the nucleophilic attack of the primary or secondary amine at the most electrophilic ring position (C(3a) and C(4a)) under formation of a very weakly stabilized intermediate **14** (Scheme 5).

This structure is of interest since the C(4a) atom involved is surrounded by four heteroatoms (three different nitrogens and a sulfur) and might therefore open a variety of different reaction channels. Most importantly, the ammonium ($N^{(+)}HR^4R^5$) moiety in **14** is situated in the neighborhood of several internal proton acceptors, i.e., at least two nitrogens and the sulfur center. We believe that the following mechanistic considerations are plausible: A proton shift resulting in **15** or **17** (other possibilities are conceivable) allows the delocalization of the lone pair (n) of the exocyclic N atom into the antibonding C−NH or C−SH bonding orbital (σ_{C-NH}* or σ_{C-SH}*). This negative hyperconjugation causes a lengthening (weakening) of the C−NH or C−SH and a shortening (strengthening) of the exocyclic N−C bond.[22] Further progress of the reaction, i.e., the preferential formation of **16** or **18**, then depends on the well-balanced stereoelectronic properties of these structures and their relative amounts in several equilibrium reactions. Weakening of the cyclic $C-N^+$ bond will cause the dihydrotriazinium ring to open, yielding **16**, the precursor of the so-called "aminals" **19**. This route has already been detected.[3] Although the basicity of the nitrogen N(4) is presumably significantly higher than that of the sulfur atom S(5), formation of a small amount of **17** (resulting from an equilibrium between **15** and **17**) could induce the second reaction channel, i.e., the opening of the fused thiadiazole ring to yield **18**.[23] The N atom of the C(9)−N(10) bond in **18** is part of a conjugated [-N(10)−C(3a)−N(4)−C(4a)−NR^4R^5]$^+$-cationic moiety. Nucleophilic attack of the sulfur center of **18** (probably after deprotonation of the SH group thus creating a more nucleophilic thiolate) and the displacement of the uncharged N(10)−C(3a)-N(4)−C(4a)−NR^4R^5-moiety (which is part of a heteroaromatic ring and is therefore an excellent leaving group)[24] causes the formation of the dihydrothiadiazole ring and finally the generation of the guanidine structures. Interestingly enough, the overall reaction can be understood as a novel example of an S_N(ANRORC) mechanism.[25]

Some mechanistic questions remain open, for example, whether a fast initial deprotonation of **14** yielding an

Scheme 5. Proposed Reaction Pathways a and b for the Transformation of 6 or 7 by Nucleophilic Attack of Amines at the C(4a) Position



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uncharged reactive carbon center with four heteroatoms dominates the reaction pathway. High level ab initio and DFT calculations under inclusion of solvent effects as well as further detailed experimental mechanistic studies addressing this questions are presently underway.

Conclusion

The new tricyclic bis(1,3,4-thiadiazolo)-1,3,5-dihydrotriazinium halides **6** and their analogues **7** are suitable precursors for the synthesis of novel guanidine derivatives. In this investigation we concentrated on the reaction behavior of some primary and secondary aliphatic amines **8** and **11** with **6** and **7**. The initial attack of nucleophiles at the C(3a) or C(4a) positions of the fused 5/6/5 heterocyclic cations are, with great certainty, not restricted to such nucleophiles. A manifold of further interesting structures resulting from **6** (and **7**) after reaction with carbon, phosphorus, or sulfur nucleophiles appears to be accessible. Theoretical ab initio and DFT investigations will allow the estimation and control of the structural and electronic properties of the crucial intermediates which determine the alternative reaction pathways a and b.

Experimental Section

General Methods. Cf. Supporting Information.

1-[Chloro-(2-hydroxyphenyl)methyl]pyridinium Chloride (3b). To a stirred solution of 0.2 mol of **2a** in MeCN (150 mL) was added 0.2 mol of pyridine under an atmosphere of argon at 0 °C followed by aldehyde **1g** (0.1 mol). The mixture was kept at 0 °C for 1 h and then allowed to warm to room temperature. After cooling to 0 °C, again 0.1 mol of MeOH was added. After heating to room temperature, the solution was concd under vacuum to 1/3 of its initial volume. The crystallization of the product **3b** was completed at 4 °C and then filtered off. The so separated crystalline pyridinium salt **3b** was pure enough for the further reactions. 68%, mp 169−172 °C.

Bis[1,3,4]thiadiazolo[3,2-*a*:3′,2′-*d*]-[1,3,5]triazinium halides 6 and 7 were prepared in MeCN from salts **3** and the heterocyclic compounds **4** and **5** according to the procedure reported in the literature.[3]

9*H*-2,6-Dimethyl-9-(2-hydroxyphenyl)-bis-[1,3,4]thiadiazolo[3,2-*a*:3′,2′-*d*]-[1,3,5] triazin-8-ium Chloride (6b). Heating **3b** and **4a** for only 5 h at 75 °C and washing the crystalline product with a little amount cold water yields **6b**: 72%, mp 214 °C.

9*H*-2,6-Diethyl-9-(2-hydroxyphenyl)-bis-[1,3,4]thiadiazolo[3,2-*a*:3′,2′-*d*]-[1,3,5]triazin-8-ium chloride (6e): analogous to **6b** from **3e** and **4b**. The solvent was removed completely under vacuum after the reaction time of 5 h. The solid residue was extracted with $CHCl_3$. The $CHCl_3$ solution was concentrated in the rotary evaporator to 1/3 of its volume. **6e**, which crystallizes from that solution within 12 h at 4 °C, was filtered off and dried under vacuum at room temperature: 82%, mp 182 °C.

9*H*-2,6-Dimethyl-9-(2-methoxyphenyl)-bis-[1,3,4]thiadiazolo[3,2-*a*:3′,2′-*d*]-[1,3,5]triazin-8-ium chloride (6f): 47% from **6f** and **4a**, mp 208−211 °C.

13*H*-13-(4-Methoxyphenyl)-bis-benzothiazolo[3,2-*a*:3′,2′-*d*]-[1,3,5]triazin-12-ium bromide (7a): 43% from **3g** and **5a**, mp 288 °C (dec).

13*H*-3,9-Dimethyl-13-(4-methoxyphenyl)-bis-benzothiazolo[3,2-*a*:3′,2′-*d*]-[1,3,5]triaz-in-12-ium bromide (7b): 37% from **3g** and **5b**, mp 264 °C (dec).

13*H*-3,9-Dimethoxy-13-(4-methoxyphenyl)-bis-benzothiazolo[3,2-*a*:3′,2′-d]-[1,3,5]tria- zin-12-ium bromide (7c): 39% from **3g** and **5c**, mp 266 °C (dec).

13*H*-3-Methyl-9-methoxy-13-(4-methoxyphenyl)-bis-benzothiazolo[3,2-*a*:3′,2′-*d*]-[1,3, 5]triazin-12-ium bromide (7d): 22% from **3g**, **5b**, and **5c**, together with **7b** (ca. 10%) and **7c** (ca. 10%) separated by crystallization, mp 253 °C (dec).

General Procedure for the Synthesis of Guanidines 9, 10, 12, and 13 from 5/6/5-Heterocycles (6 or 7) and Amines (8 or 11). To a stirred suspension of 5 mmol of **6** or **7** in pyridine (60 mL)[26] was added 10.1 mmol of **8a**−**f** or **11** at room temperature. After stirring of this mixture at room temperature (24 h), the nearly clear solution was concd to dryness under vacuum. From the residue the amine HX byproduct and some pyridine were washed off with water. The solid products were recrystallized from MeOH/*tert*-butyl methyl ether. Oily products were dissolved in $CHCl_3$ and purified by column chromatography (silica gel 60, 0.063−0.2 mm, ethyl acetate).

(*E*)-1-[(5-Methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(4-methylphenyl)-5-methyl-1,3,4-thiadiazol-3-yl]methylpiperidine (9a): 85%, mp 142−143 °C.

(*E*)-4-[(5-Methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(4-methylphenyl)-5-methyl-1,3,4-thiadiazol-3-yl]methylmorpholine (9b): 68%, mp 84 °C.

(*E*)-1-[(5-Methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(4-methylphenyl)-5-methyl-1,3,4-thiadiazol-3-yl]methylpyrrolidine (9c): 70%; 83% (rough), mp 74 °C (dec); **9c** •2 HBF_4 salt mp 135 °C (dec).

(*E*)-[(5-Methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(4-methylphenyl)-5-methyl-1,3,4-thiadiazol-3-yl]methyl-diethylamine (9d): 70%, oil.

(*E*)-1-[(5-Methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(2-hydroxyphenyl)-5-methyl-1,3,4-thiadiazol-3-yl]methylpyrrolidine (9e): 87%, mp 148 °C.

(*E*)-4-[(5-Methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(2-hydroxyphenyl)-5methyl-1,3,4-thiadiazol-3-yl]methylmorpholine (9f): 85%, mp 124 °C.

(*E*)-1-[(5-Methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(1-naphthyl)-5-methyl-1,3,4-thiadiazol-3-yl]methylpiperidine (9g): 68%, mp 149−150 °C.

(*E*)-4-[(5-Methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(1-naphthyl)-5-methyl-1,3,4-thiadiazol-3-yl]methylmorpholine (9h): 90%, mp 152−153 °C.

(*E*)-1-[(5-Methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(1-butyl)-5-methyl-1,3,4-thiadiazol-3-yl]methylpiperidine (9i): 95%, oil.

(*E*)-4-[(5-Methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(1-butyl)-5-methyl-1,3,4-thiadia- zol-3-yl]methylmorpholine (9j): 90%, oil.

(*E*)-1-[(5-Ethyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(2-hydroxyphenyl)-5-ethyl-1,3,4-thiadiazol-3-yl]methylpyrrolidine (9k): 84%, mp 127 °C.

(*E*)-4-[(5-Ethyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(2-hydroxyphenyl)-5-ethyl-1,3,4-thiadiazol-3-yl]methylmorpholine (9l): 89%, mp 144 °C (dec).

(*E*)-[(5-Methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(4-methylphenyl)-5-methyl-1,3,4-thiadiazol-3-yl]methyl-butylamine (9m): 74%, mp 97 °C.

(*E*)-[(5-Methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(1-naphthyl)-5methyl-1,3,4-thiadiazol-3-yl]methyl-butylamine (9n): 77%, mp 134−135 °C.

(*E*)-[(5-Methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(1-butyl)-5-methyl-1,3,4-thiadiazol-3-yl]methyl-butylamine (9o): 80%, oil.

(*E*)-[(5-Ethyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(2-hydroxyphenyl)-5-ethyl-1,3,4-thiadiazol-3-yl]methyl-(2-pyridin-2-yl-ethyl)amine (9p): 81%, mp 150 °C.

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(26) Instead of pyridine, triethylamine, THF, and *tert*-butyl methyl ether can be used as solvents as well.

(*E*)-1-[(Benzothiazol-2-yl)imino]-[2*H*-2-(4-methoxyphenyl)benzothiazol-3-yl]methyl-piperidine (10a): 90%, mp 147−149 °C.

(*E*)-4-[(Benzothiazol-2-yl)imino]-[2*H*-2-(4-methoxyphenyl)benzothiazol-3-yl]methyl-morpholine (10b): 91%, mp 176 °C.

(*E*)-1-[(Benzothiazol-2-yl)imino]-[2*H*-2-(4-methoxyphenyl)benzothiazol-3-yl]methyl-pyrrolidine (10c): 90%, mp 177−180 °C (dec).

(*E*)-[(Benzothiazol-2-yl)imino]-[2*H*-2-(4-methoxyphenyl)-benzothiazol-3-yl]methyl-(2-pyridin-2-yl-ethyl)amine (10d): 86%, mp 90 °C (dec).

(*E*,*E*)-1,4-Bis-[[(5-methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(4-methylphenyl)-5-methyl-1,3,4-thiadiazol-3-yl]-methylpiperazine (12a): 79%, mp 192 °C (MeOH) (meso form 2*R*,2′*S*), mp 177 °C (racemic 2*R*,2′*R* and 2*S*,2′*S*).

(*E*,*E*)-1,4-Bis-[[(5-methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(1-naphthyl)-5methyl-1,3,4-thiadiazol-3-yl]methylpiperazine (12b): 94%, mp 242 °C (MeOH), (meso form 2*R*,2′*S*), mp 157 °C (MeOH), (racemic 2*R*,2′*R* and 2*S*,2′*S*).

(*E*,*E*)-1,4-Bis-[[(5-methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(1-butyl)-5-methyl-1,3,4-thiadiazol-3-yl]methylpiperazine (12c): 88%, mp 108−109 °C (isomeric mixture).

(*E*,*E*)-1,4-Bis-[[(5-methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(2-hydroxyphenyl)-5-methyl-1,3,4-thiadiazol-3-yl]-methylpiperazine (12d): 85%, mp 168−169 °C (isomeric mixture).

(*E*,*E*)-1,4-Bis-[[(5-methyl-1,3,4-thiadiazol-2-yl)imino]-[2*H*-2-(2-methoxyphenyl)-5-methyl-1,3,4-thiadiazol-3-yl]-methylpiperazine (12e): 82%, mp 178−180 °C (isomeric mixture).

(*E*,*E*)-1,4-Bis[(Benzothiazol-2-yl)imino]-[2*H*-2-(4-methoxyphenyl)benzothiazol-3-yl] methylpiperazine (13): 90%, mp 237 °C (isomeric mixture).

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Supporting Information Available: General methods; data of ^{1}H NMR, ^{13}C NMR, MS, elemental analyses for the compounds **3b**, **6b**, **6e**, **6f**, **7a**−**d**, **9a**−**p**, **10a**−**d**, **12a**−**e**, **13**; crystal structure determination and crystal data for **9a**, **9n**, **12a** (*R*,*R*)-isomer, **12a**·2MeOH (meso isomer) as well as the corresponding crystal structures (Figure 5: **9a**; Figure 6: **9n;** Figure 7: (*R*,*R*)-isomer of **12a**). This material is available free of charge at http://pubs.acs.org.

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