# Progress in 1,2,3,4-Tetrazine Chemistry

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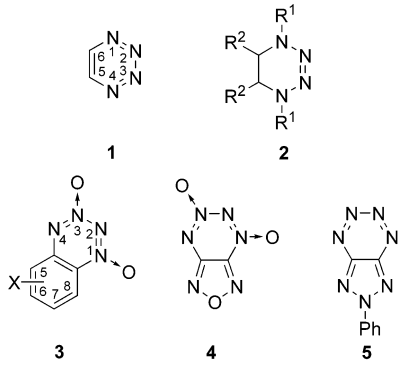
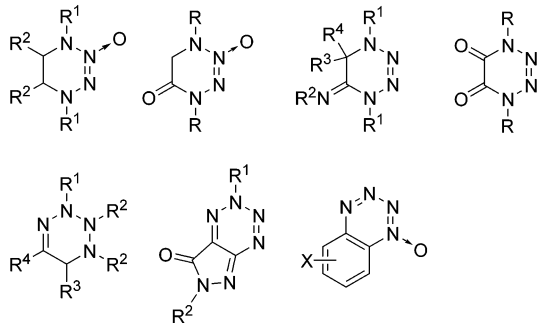
## *1. Introduction*

This review covers the derivatives of 1,2,3,4-terazine **1**, including tetrazines annulated through the C5−C6 bond and including partly reduced systems. Fused systems with ring-junction nitrogen atoms are not considered.

The first representatives of the 1,2,3,4-tetrazine ring system, the structure of which was unambiguously proved, were tetrahydro-1,2,3,4-tetrazines of type **2**, which were synthesized in 1971 by Kreher and Wi$\beta$mann[1] and shortly afterward by Nelson and Fibinger.[2] The first representatives of fully unsaturated tetrazines, i.e., annulated 1,2,3,4-tetrazine 1,3-dioxides **3** and **4,** were synthesized in 1984 by the authors of this review and Ioffe. However, the results of that study were published in available journals only in 1990 for 1,2,3,4-benzotetrazine 1,3-dioxides **3**[3] (referred to as "benzotetrazine 1,3-dioxides" or BTDOs later) and in 1995 for [1,2,5]oxodiazolo-[3,4-*e*][1,2,3,4]tetrazine 4,6-dioxide **4**.[4] In 1988, Ohsawa and co-workers synthesized the first fully unsaturated triazolo-annulated 1,2,3,4-tetrazine **5**.[5]



The 1,2,3,4-tetrazine literature was reviewed in a monograph of Benson[6] and in the first[7] and second[8] additions of *Comprehensive Heterocyclic Chemistry*. The latter review covers the literature to early 1994. In addition to systems **2**−**5**, further 1,2,3,4-tetrazine systems had been described at that time.



This review covers the literature published from 1994 up to the early part of 2003. Earlier material is included here only where needed as a basis for describing further developments. In the past decade, 1,2,3,4-tetrazines have attracted considerable attention. The 2*H*-cyclopenta[*e*][1,2,3,4]tetrazine/(arylazo)-diazocyclopentadiene **6**/**7** equilibrium has been described[9] (eq 1).

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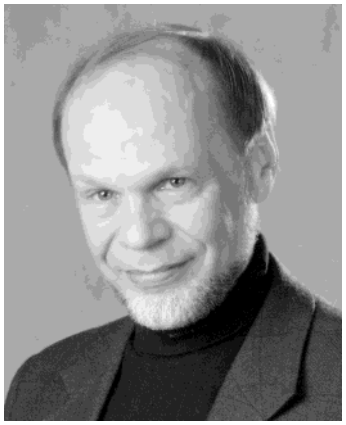
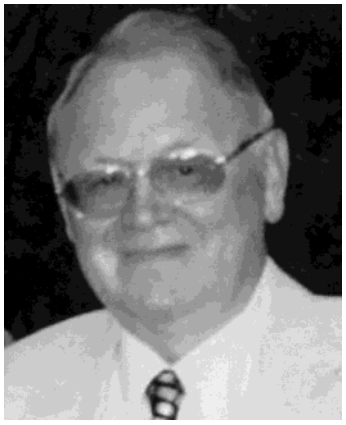
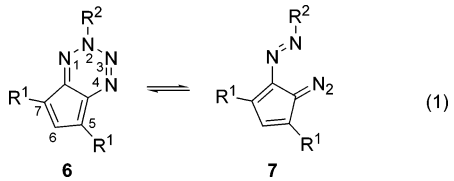


Aleksandr M. Churakov was born in Moscow, Russia, in 1951. He graduated from the Mendeleev Russian University of Chemical Technology in 1975. Since then he has been working at the Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences (Moscow), where he received his Ph.D. degree in organic chemistry in 1983. His main research interests are focused on nitrogen heterocyclic chemistry, specifically high-nitrogen compounds, their structure, and new methods of N–N bond formation in their synthesis.

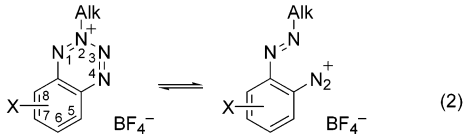


Vladimir A. Tartakovsky was born in Moscow, Russia, in 1932. He graduated from the Chemistry Department of Moscow State University in 1955. Since 1955 he has been working at the Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences (RAS). Since 1971 he has been Head of the Laboratory of Nitro Compounds Chemistry. He is Professor of Chemistry and a Full Member of the Russian Academy of Sciences. From 1988 to 2003 he held the post of Director of the Institute. He is primarily involved in the chemistry of nitro compounds, including development of new nitration methods and approaches to nitro compound applications in organic synthesis. However, his scientific interest extends over the area of new linear and cyclic polynitrogen–oxygen systems. He is a world leader in the field of high energy materials.



**6** **7** (1)

The 2-alkyl-1,2,3,4-benzotetrazinium/(alkylazo)-benzenediazonium **8/9** equilibrium has also been reported[10] (eq 2).

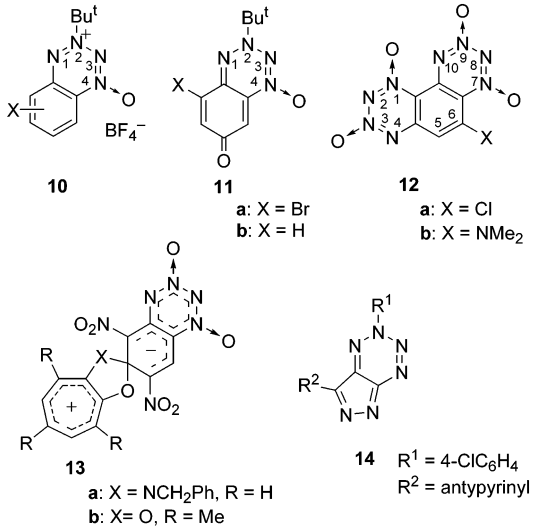


**8** **9** (2)

| | Alk | X |
|---|---|---|
| **8a/9a** | *t*-Bu | H |
| **8b/9b** | *t*-Bu | 7-Br |
| **8c/9c** | *t*-Bu | 6-Br |
| **8d/9d** | *t*-Bu | 7-Me |
| **8e/9e** | *t*-Bu | 6-Me |

| | Alk | X |
|---|---|---|
| **8f/9f** | *t*-Bu | 5,7-$Br_2$ |
| **8g/9g** | *t*-Bu | 5,7-$Cl_2$ |
| **8h/9h** | Me | H |
| **8i/9i** | Me | 5,7-$Br_2$ |

The following novel tetrazine systems have been synthesized: 2-(*tert*-butyl)-benzotetrazinium tetrafluoroborate 4-oxides **10**,[11,12] 2-(*tert*-butyl)-benzotetrazin-6(2*H*)-one 4-oxides **11**,[11,12] [1,2,3,4]tetrazino[5,6-*f*]-[1,2,3,4]benzotetrazine 1,3,7,9-tetraoxides **12**,[13] bipolar spiro-$\sigma$-complexes **13**,[14] and 2*H*-pyrazolo[3,4-*e*][1,2,3,4]-tetrazine **14**.[15] The chemistry of benzotetrazine 1,3-dioxides **3** was developed. During this period, no aromatic monocyclic 1,2,3,4-tetrazines have been described.



**10** **11** **12**

**a**: X = Br
**b**: X = H

**a**: X = Cl
**b**: X = $NMe_2$

**13**

**a**: X = $NCH_2Ph$, R = H
**b**: X= O, R = Me

**14** $R^1$ = 4-$ClC_6H_4$
$R^2$ = antypyrinyl

## 2. Theoretical Methods

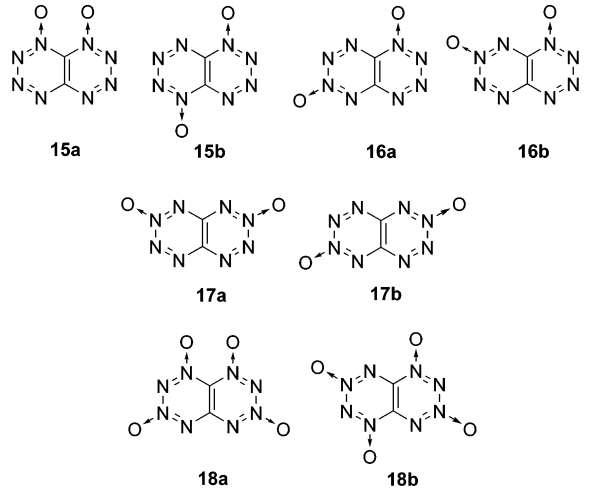
A MO multicenter bond index ($I_{ring}$) involving the $\sigma + \pi$ electron population is proposed as a measure of aromaticity.[16] It is related to both the energetic and the magnetic criteria. The index is applied to monocyclic azines, including 1,2,3,4-tetrazine **1**. All monocyclic azines have $I_{ring}$ close to that of benzene.

A review on quantitative measure of aromaticity for heteroatomic ring systems, including 1,2,3,4-tetrazine, was published recently.[17]

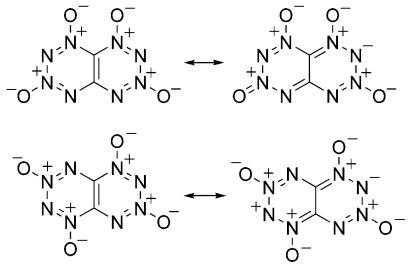
Ab initio (RHF/6-31G**) heats of formation of azines, including 1,2,3,4-tetrazine **1** ($\Delta H_f$ = 133.5 kcal/mol), have been calculated using isolobal reaction schemes.[18] The ab initio heats of formation are compared with calculated semiempirical (MNDO, AM1, PM3) heats of formation. All three semiempirical methods systematically underestimate heats of formation, PM3 being the most accurate. Correction terms for the semiempirical azine heats of formation are suggested, which bring semiempirical values into agreement with experimental results.

The relative stabilities of hypothetical [1,2,3,4]-tetrazino[5,6-*e*][1,2,3,4]tetrazine *N*-oxides **15**−**18** have been discussed.[19] On the basis of the heats of formation (MNDO), the dioxides **15a**, **16a,** and **17a** are more stable than the isomeric dioxides **15b**, **16b,** and **17b**. The tetraoxide **18a** is more stable than the isomeric tetraoxide **18b** (MNDO, $\Delta\Delta H_f \approx 11$ kcal/mol;

PM3, $\Delta\Delta H_f \approx 16$ kcal/mol). The higher stability of **a**-isomers compared with **b**-isomers is due to a difference in the topology of the molecules.



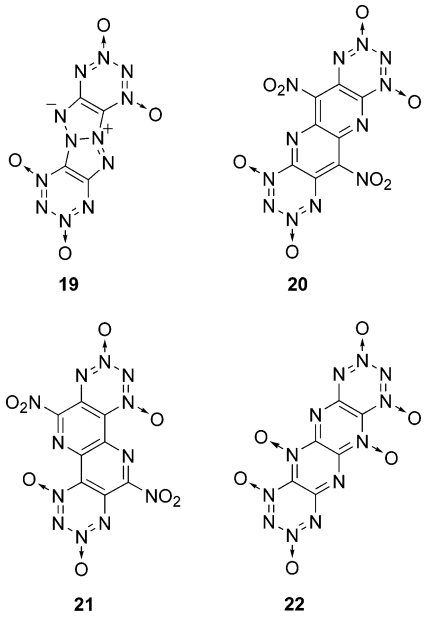

The characteristic features of isomers **a**, compared with isomers **b**, are the lower calculated (MNDO) HOMO energies and pronounced alternation of charges on adjacent atoms.[19] This alternation is evident from the following resonance structures.



The related resonance structures could explain the spectral and chemical features of substituted benzotetrazine 1,3-dioxides (see below). Note that real thermal stabilities of compounds **15**−**17** might be very low in contrast to the one of **18**, which might be much higher (see section 7.2).

A number of hypothetical compounds, including compounds **19**−**22** containing the tetrazine dioxide ring system, resulted from a computer-aided search for the structures of hydrogen-free high-density compounds with high energy content.[20] The structures and energies of molecules in the gas phase were calculated according to semiempirical methods (MNDO and PM3). Calculation of the crystal structure, sublimation enthalpy, and molecular crystal density of compounds were conducted using the method of Atom−Atom Potential Functions. According to calculations, the densities of compounds are equal to 1.90 g·cm$^{-3}$ for **19** and 2.00−2.01 g·cm$^{-3}$ for **20**−**22**.

MRINDO/S calculations of the electronic spectra completed by singly excited configuration interaction were performed on the triazines and tetrazines, including 1,2,3,4-tetrazine **1**. Ionization potentials of the azines were interpreted.[21] Ab initio, second-order, Moller−Plesset perturbation theory calculations of quadrupole and octopole moments were reported for 36 different 6$\pi$-electron monocycles, including 12

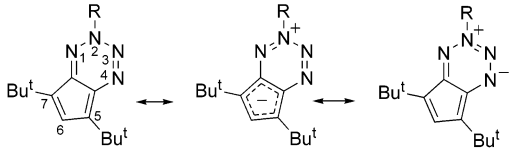



azines, 1,2,3,4-tetrazine **1** among them.[22] Ab initio studies of the geometries, dipole moments, and static dipole polarizabilities are reported for the 12 monocyclic azines, including 1,2,3,4-tetrazine **1**, at the Hartree−Fock and d-functional (BLYP) levels of theory.[23] Semiempirical PM3 dipole-polarizability calculations are also reported for comparison. To a good approximation, the mean value of the dipole polarizability depends only on the number of N (or C) atoms in the ring and not on their relative positions within the ring.[23] Geometries, dipole moments, and static dipole polarizabilities for the 12 monocyclic azines including 1,2,3,4-tetrazine **1** were also obtained at the Hartree−Fock level.[24]

## *3. Experimental Structural Methods*

### 3.1. X-ray Analysis

The X-ray data of 5,7-di-*tert*-butyl-2-R-2*H*-cyclopenta[*e*]-1,2,3,4-tetrazines **6a** and **6b** indicate the planar geometry of this bicyclic system.[9] The C−C bond lengths are in good accordance with other structures containing a five-membered carbocycle as a part of an aromatic bicycle (e.g., azulene). In the six-membered rings, the N−N distances are in the range of the typical values for localized N−N single and double bonds (Table 1) due to conjugation, reflected by the following resonance structures.



**6**

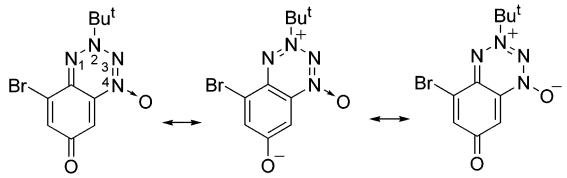
**a**: R = 4-$CH_3OC_6H_4$
**b**: R = Me

The N1−N2 distances (Table 1) are similar to those of related hydrazones, and the N2−N3 and N3−N4 distances are similar to the appropriate distances of triazenes.

**Table 1. Selected Bond Lengths (Å) in Compounds 6a, 6b, and 11a**

| compd | C−N1 | N1−N2 | N2−N3 | N3−N4 | C−N4 | ref |
|---|---|---|---|---|---|---|
| **6a** | 1.305 | 1.320 | 1.363 | 1.300 | 1.359 | 9 |
| **6b** | 1.312 | 1.328 | 1.358 | 1.300 | 1.344 | 9 |
| **11a** | 1.33 | 1.32 | 1.34 | 1.31 | 1.44 | 11 |

X-ray analysis of 8-bromo-2-(*tert*-butyl)-benzotetrazin-6(2*H*)-one 4-oxide **11a** shows that the bicyclic system of this molecule is also planar,[11] which implies a considerable contribution of the resonance forms, similar to those of compounds **6a** and **6b**.



**11a**

The bond lengths in the tetrazine ring of molecule **11a** are close to those in compounds **6a**,**b** with the difference being that the N2−N3 bond is shorter, the N3−N4s is slightly longer, and the C−N4 bond is much longer (Table 1). This fact indicates the more efficient resonance of the triazene oxide N2−N3−N4(O) fragment of molecule **11** as compared with the triazene N2−N3−N4 fragment of molecules **6**.

## 3.2. $^1$H and $^{13}$C NMR Spectroscopy

In the cyclopenta[*e*][1,2,3,4]tetrazine/(arylazo)diazocyclopentadiene **6**/**7** mixtures (eq 1), both isomers are detected by $^1$H NMR spectroscopy.[9] Though these spectra cannot prove the structures directly, the signals of the protons of the five-membered ring allow differentiating isomers **6** and **7**. For example, the H-6 signals of **6c** are detected at the aromatic region, whereas the appropriate signals of the open-chain tautomer **7c** show a strong upfield shift, demonstrating the olefinic character (Figure 1). Hence, the chemical shifts support the existence of a diamagnetic ring current for the bicyclic system **6**.

The tetrazinium−azodiazonium **8** ⇆ **9** equilibrium (eq 2) is fast on the NMR time scale, and only one set of signals is observed in the $^1$H and $^{13}$C NMR spectra even at low temperatures.[10] The chemical shifts of the *tert*-butyl or methyl protons were used to estimate the relative amount of the cyclic and open-chain forms. 2-(*tert*-butyl)-5,7-dibromobenzotetrazinium tetrafluoroborate **8f** exists entirely in the cyclic form. The signal of its *tert*-butyl group is observed at $\delta$ = 2.16 ppm. In contrast, 2-(*tert*-butylazo)-3-pyridinediazonium tetrafluoroborate **23**

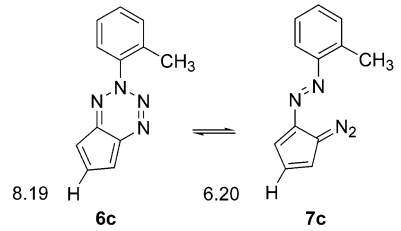


**Figure 1.** $^1$H NMR chemical shifts ($\delta$, ppm).

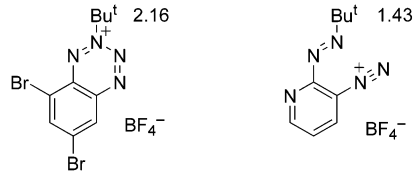


**Figure 2.** $^1$H NMR chemical shifts of the *tert*-butyl groups ($\delta$, ppm).

**Table 2. $^1$H NMR Assignments for Benzotetrazine 1,3-Dioxide 3a in Acetone-$d_6$**

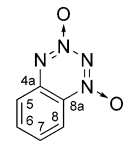
| | proton | | | |
|---|---|---|---|---|
| | H-5 | H-6 | H-7 | H-8 |
| $\delta_H$ | 7.92 m | 8.18 m | 7.91 m | 8.35 m |
| $J$ [Hz] | $^3J(5,6) = 8.5$ | $^3J(6,7) = 7.1$ | $^3J(7,8) = 8.6$ | $^4J(8,6) = 1.3$ |
| | | | $^4J(7,5) = 1.3$ | $^5J(8,5) = 0.6$ |

**Table 3. $^{13}$C NMR Assignments for Benzotetrazine 1,3-Dioxide 3a in Acetone-$d_6$**

| | | $J_{C,H}$ (Hz) | | | |
|---|---|---|---|---|---|
| carbon | $\delta_C$ | H-5 | H-6 | H-7 | H-8 |
| C-4a | 144.7 | $^2J = 1.5$ | $^3J = 10.2$ | $^4J = 0$ | $^3J = 5.0$ |
| C-5 | 125.2 | $^1J = 171$ | $^2J = 1.5$ | $^3J = 7.6$ | $^4J = -1.3$ |
| C-6 | 139.2 | $^2J = 0.5$ | $^1J = 166$ | $^2J = 1.7$ | $^3J = 8.7$ |
| C-7 | 132.3 | $^3J = 8.7$ | $^2J = 1.2$ | $^1J = 169$ | $^2J = -0.3$ |
| C-8 | 119.9 | $^4J = -1.3$ | $^3J = 7.8$ | $^2J = 1.9$ | $^1J = 174$ |
| C-8a | 129.0 | $^3J = 6.7$ | $^4J = 1.5$ | $^3J = 10.5$ | $^2J = 2.6$ |

exists entirely in the open-chain form, and its *tert*-butyl group shows a signal at $\delta$ = 1.43 ppm. The *tert*-butyl signals of salts **8**/**9** bearing various substituents at the benzene ring (see Table 9), the solutions of which contain both cyclic and open-chain forms, are located between these two extremes, and simple calculations allow determining the percentage of the cyclic forms in the equilibrium mixtures[10] (see section 4, Table 9). The $^1$H NMR temperature studies of the **6** ⇆ **7**[9] as well as the **8** ⇆ **9**[10] equilibrium showed that the amount of cyclic form tended to increase with a decrease in temperature. For the process **6c** ⇆ **7c** (Figure 1), a free activation energy of $\Delta G^{\ddagger}$ (333 K) = 72.1 ± 1 kJ/mol has been determined by line-shape analysis.[9]

The $^1$H and $^{13}$C NMR spectral data for the parent benzotetrazine 1,3-dioxide **3a** are listed in Tables 2 and 3, respectively.[25,26]



**3a**

The $^{13}$C chemical shifts of benzotetrazine 1,3-dioxide **3a** were compared with the ones of benzene ($\delta_{benzene}$ = 128.7 ppm). With regard to the effect of the tetrazine 1,3-dioxide ring on the benzene ring carbons, the most downfield shifts are due to the C-4a and C-6 carbons and the most upfield shift is due to the C-8 carbon, whereas the C-8a chemical shift remains practically unchanged (Figure 3).

The C,H coupling constants of the benzotetrazine 1,3-dioxide were measured (Table 3). The values of

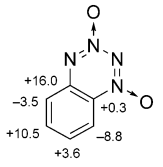
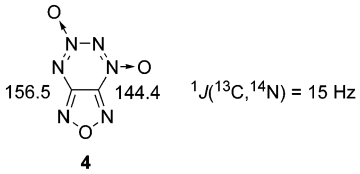



**Figure 3.** Shifts of $\delta(^{13}C)$ compared with $\delta(^{13}C)$ of benzene in acetone-$d_6$.



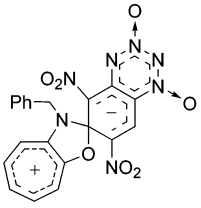

**4**

**Figure 4.** $^{13}C$ NMR assignments for **4**.

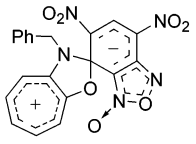
long-range coupling constants $^3J$(H-5,C-8a) and $^3J$(H-8,C-4a) are rather small (6.7 and 5.0 Hz, respectively). This observation could help in assignment of $^{13}C$ signals of substituted benzotetrazine 1,3-dioxides.

The $^{13}C$ NMR spectra of furazano-annulated tetrazine 1,3-dioxide **4** in acetone-$d_6$ is shown in Figure 4.[4] The signal of the carbon linked with the *N*-oxide nitrogen atom is a triplet due to the carbon−nitrogen coupling. In a benzotetrazine 1,3-dioxide series, the related C-8a signals are broadened due to the same coupling. This broadening can be suppressed by $^{13}C\{^{14}N\}$ experiments.

The $^1H$ NMR spectra of the bipolar spiro-$\sigma$-complex **13a** showed the AB quartet from the methylene protons of the diastereotopic $PhCH_2N$ group (see the Introduction).[14] When this chiral complex was heated in $C_6D_5NO_2$, the AB quartet was reversibly converted to a singlet, indicating the *R,S*-enantiotopomerization, whose kinetic and activation parameters were determined. Attention is drawn to the fact that the kinetic stability of **13a** ($k_{298} = 1.2 \times 10^1$ in $C_6D_5NO_2$) is much lower than that of the spiro-$\sigma$-complex of 4,6-dinitrofuroxane **24** ($k_{298} = 5 \times 10^{-5}$ in DMSO-$d_6$). This probably is due to the higher aromaticity of the benzotetrazine 1,3-dioxide system as a whole relative to the dinitrobenzofuroxane system rather than to a difference in the electron-withdrawing properties of the furoxane and tetrazine 1,3-dioxide rings.



**13a**

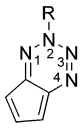


**24**

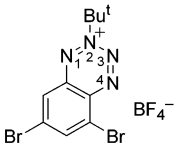
## 3.3. Nitrogen NMR Spectroscopy

Nitrogen NMR spectroscopy is a direct method for ascertaining the tetrazine structures. It is especially useful for studying the ring-chain tautomerism. For the pair of azodiazo/tetrazine tautomers **6c**/**7c** (Figure 1), both tautomeric forms are observed by $^{15}N$ NMR spectroscopy in DMSO at 20 °C. Whereas the N-1 and N-2 atoms of isomer **7c** gave rise to resonances in the range typical of azo nitrogen atoms (80−100 ppm), these signals of isomer **6c** are shifted upfield over 100 ppm (Table 4). The assignment for the pyrrole-like nitrogen N-2 was based on chemical shifts of related compounds. Samples of **6c** and **6d** labeled with $^{15}N$ in positions 1 and 4 enable the signal assignment for the N-1 and N-4 atoms, respectively.[9]

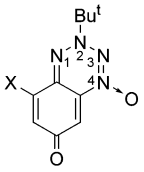
**Table 4. $^{15}N$ Chemical Shifts[a] of Annulated 2-R-1,2,3,4-Tetrazines[b]**



**6c**: R = 2-$CH_3C_6H_4$
**6d**: R = Ph



**8f**



**11a**: X = Br
**11b**: X = H

| compd | N-1 | N-2 | N-3 | N-4 | ref |
|---|---|---|---|---|---|
| **6c** | −48.4 | −124.9 | −14.5 | −22.7 | 9 |
| **6d** | −57.0 | −124.5 | −19.03[c] | −19.43[c] | 9 |
| **8f**[d] | | −134.1 | | | 10 |
| **11a** | −62.6 | −127.5 | −40.2 | −77.1 | 11 |
| **11b** | −60.3 | −127.0 | −40.8 | −74.6 | 11 |

[a] Here and below, chemical shifts are given from external $MeNO_2$; negative values correspond to upfield shifts. [b] Solvent DMSO-$d_6$ for **6c**,**d** and **11a**,**b**, and acetone-$d_6$ for **8f**. [c] Assignments may be interchanged. [d] At 273 K.

The $^{14}N$ NMR spectra of **11a,b** showed narrow signals due to N-4 nitrogen (acetone-$d_6$, for **11a** $\delta = -77$, $\Delta\nu_{1/2} = 70$ Hz; for **11b** $\delta = -74$, $\Delta\nu_{1/2} = 80$ Hz), whereas the $^{15}N$ NMR spectrum reveals all four nitrogens (Table 4). For **11a,** the assignments of N-2 ($^3J(H,^{15}N) \approx 2.8$ Hz) and the pair of N-1 and N-3 atoms ($^4J(H,^{15}N) \approx 0.5$ Hz) were based on INEPT experiment. The alternative in assignments for N-1 and N-3 nitrogens were based on chemical shifts of related hydrazone and triazene oxide systems.[11]

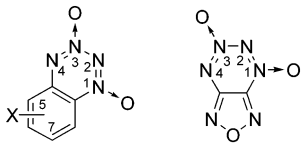
In contrast to the **6** ⇆ **7** equilibrium, the **8** ⇆ **9** equilibrium is fast on the NMR time scale. For **8f** it was entirely shifted in favor of the cyclic form, which was confirmed by the $^{15}N$ NMR/INEPT spectrum. The nitrogen attached to the *tert*-butyl group was observed in the region typical of related structures (Table 4).

The open-chain form for pyridinediazonium salt **23** was confirmed by its $^{14}N$ NMR spectrum ($\delta = -195$ ppm, $-N{\equiv}N^+$) and by its $^{15}N$ NMR/INEPT spectrum at 250 K, which showed a signal typical of the azo group at $\delta = 208.6$ ppm ($-N{=}N{-}Bu^t$).[10]

The $^{15}N$ NMR of benzotetrazine-1,3-dioxides **3** showed four signals (Table 5). The signal assignments were based on the selective polarization transfers (SPTs) from the H-5 and H-8 protons of the parent benzotetrazine 1,3-dioxide **3a** as well as on the spectra of the samples of 7-nitrobenzotetrazine 1,3-dioxide and 5,7-dinitrobenzotetrazine 1,3-dioxide labeled with $^{15}N$ in position 3.[25,26]

The study of a large number of benzotetrazine-1,3-dioxids **3** (X = Br, Cl, $N_3$, $NMe_2$, $NO_2$, OMe) showed that the tetrazine-1,3-dioxide system could easily be identified by $^{14}N$ NMR examination.[13,25,26] Most of compounds investigated showed two narrow signals in the acetone or chloroform solutions with $\delta$(N-1) = −40 to −43 ppm ($\Delta\nu_{1/2} = 35-40$ Hz) and $\delta$(N-3) = −45 to −49 ppm ($\Delta\nu_{1/2} = 45-70$ Hz). The signals of

**Table 5. $^{15}$N Chemical Shifts of Annulated 1,2,3,4-Tetrazine 1,3-Dioxides 3 and 4**



3



4

| compd | X | N-1 | N-2 | N-3 | N-4 |
|---|---|---|---|---|---|
| **3a**[a] | H | −41.0 | −23.9 | −48.7 | −81.9 |
| **3b**[b] | 7-$NO_2$ | −40.3 | −21.0 | −46.3 | −83.3 |
| **3c**[b] | 5,7-$(NO_2)_2$ | −41.2 | −19.5 | −45.8 | −92.9 |
| **4**[a] | | −52.7 | 8.0 t[c] | −43.9 | −106.0 |

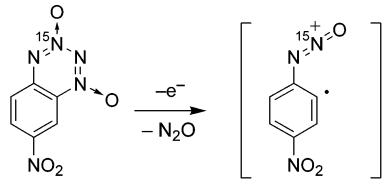
[a] In acetone-$d_6$. [b] In DMSO-$d_6$. [c] $^1J(^{14}N\text{-}1,^{15}N\text{-}2) = 20$ Hz.

the N-2 and N-4 nitrogens are rather wide ($\Delta\nu_{1/2} >$ 400 Hz), and as a rule they are not observed.

The structure of furazano-annulated tetrazine 1,3-dioxide **4** was proved with the help of $^{14}$N and $^{15}$N NMR of samples labeled with $^{15}$N in position 3 as well as in positions 1 and 3 and also in position 3 and 4.[4] The signal of the N-3 nitrogen was only slightly different from its counterpart in the benzo-annulated tetrazine 1,3-dioxide system, whereas the N-1 and N-4 signals were shifted upfield, and the N-2 signal exhibited a strong downfield shift (Table 5). It should be noted that the $^{14}$N signal of the *N*-oxide N-1 nitrogen is uncommonly sharp, causing a distinct splitting of the signals of the neighboring $^{13}$C carbon and $^{15}$N nitrogen atoms.

## 3.4. Mass Spectrometry

The electron impact mass spectra of benzo- and furazano-annulated tetrazine 1,3-dioxides display the molecular ion peaks. Benzotetrazine 1,3-dioxides undergo fragmentation that includes a stepwise loss of $N_2O$ molecules, giving peaks corresponding to $[M - N_2O]^+$ and $[M - 2N_2O]^+$. Study of the 7-nitrobenzotetrazine 1,3-dioxide labeled with $^{15}$N in the 3-position showed that the $^{15}$N atom was retained in the molecule after the loss of the first $N_2O$ molecule.[26] The fragmentation pathway of furazano-annulated tetrazine 1,3-dioxide **4** includes the simultaneous loss of two $N_2O$ molecules.[4]



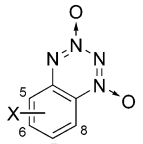

*m/z* 210 *m/z* 166

## 3.5. UV Spectroscopy

Annulated 1,2,3,4-tetrazine 1,3-dioxides **3** show an absorption band in the visible region, indicative of efficient conjugation in the tetrazine 1,3-dioxide ring system (Table 6).

As a result of an experimental and theoretical study (CNDO/S method), electron transitions in the tetrazine dioxide fragment were identified.[27] The bands localized in the 300−390 and 410−550 nm regions are due to the $\pi-\pi^*$ and $n-\pi^*$ transitions in this fragment, respectively (Table 6). The bands at 200−300 nm ($\epsilon$ ca. $10^4$ to $2 \times 10^4$) are due to transitions with the intramolecular charge transfer from the $\pi$ orbital of the benzene ring to the antibonding orbital of the tetrazine dioxide fragment.

**Table 6. UV Spectra of Benzotetrazine 1,3-Dioxides 3**



3

| X | transition | $\lambda_{max}$/nm | $\epsilon$ |
|---|---|---|---|
| H | $\pi-\pi^*$ | 310[a] | |
| | $n-\pi^*$ | 420 | 1700 |
| 7-MeO | $\pi-\pi^*$ | 337 | 7000 |
| | $n-\pi^*$ | 453 | 3200 |
| 6-Meo | $\pi-\pi^*$ | 300[a] | |
| | $n-\pi^*$ | 408 | 3300 |
| 7-$Me_2N$ | $\pi-\pi^*$ | 388 | 9300 |
| | $n-\pi^*$ | 545 | 2200 |
| 6-$Me_2N$ | $\pi-\pi^*$ | 345 | 3500 |
| | $n-\pi^*$ | 470 | 2700 |

[a] Inflection.

The UV spectra of 2*H*-cyclopenta[*e*]-1,2,3,4-tetrazines **6** have been recorded.[9]

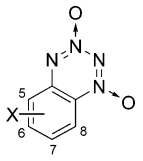
## 3.6. IR Spectroscopy

The study of vibrational spectra of annulated tetrazine 1,3-dioxides **3** and **4** showed that there was a strong vibrational interaction between two diazene oxide groups of the tetrazine 1,3-dioxide moiety.[28,29] The detailed assignments of vibrational spectra of furazano-annulated 1,2,3,4-tetrazine 1,3-dioxide **4** were based on comparison of its IR and Raman spectra with the recording of the degree of depolarization of the bands and a calculation of the frequencies and forms of the normal vibrations of **4** and its [$^{15}$N-3]isotopically substituted derivative. The bands with $\nu = 1548$ and 1420 $cm^{-1}$ were assigned to stretching vibrations of the tetrazine dioxide moiety. These vibrations occur with predominant participation of the N═N bonds. Since in the first one the two N═N bonds vibrate in phase and in the second in antiphase, these vibrations were approximately considered as synphase ($\nu^{syn}$(N═N)) and antiphase ($\nu^{ansyn}$(N═N)) vibrations, respectively. The participation of the single N−N bonds and N→O bonds in these vibrations is weak. These vibrations give an intense absorption in the IR spectrum, but in the Raman spectrum their bands are weak, polarized and depolarized, respectively.

The characteristic peaks of the tetrazine 1,3-dioxide moiety in the IR spectrum of substituted benzotetrazine 1,3-dioxides **3** are listed in Table 7. The assignments for the 7-$NO_2$-substituted derivative were confirmed by the IR spectrum of the [$^{15}$N-3]-isotopically substituted sample.

IR spectroscopy was used for the study of azo-diazo−tetrazino isomerism.[9]

**Table 7. Stretching Vibrations of Benzotetrazine 1,3-Dioxides 3 ($\nu$/cm$^{-1}$)**

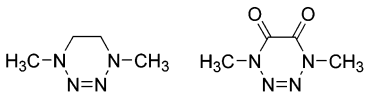


3

| X | $\nu^{syn}$(N=N) | $\nu^{ansyn}$(N=N) |
|---|---|---|
| H | 1497 s | 1402 s |
| 7-Meo | 1486 s | 1404 m |
| 6-Meo | 1496 s | 1424 s |
| 7-$Me_2N$ | 1468 s | 1404 m |
| 6-$Me_2N$ | 1474 s | 1408 s |
| 7-$NO_2$ | 1517 s | 1431 s |
| 5-$NO_2$ | 1507 s | 1428 s |
| 5,7-$(NO_2)_2$ | 1520 s | 1432 s |

## 3.7. Photoelectron Spectra

The photoelectron (PE) spectra of tetrahydro-1,2,3,4-tetrazines **25** were analyzed with respect to the conformational properties of this molecule.[30] According to ab initio HF and Becke3LYP calculations, tetrazine **25** possesses two low-energy conformations, i.e., half-chair and unsymmetrical boat conformations. Both conformers are present in the gas phase. However, ionizations arising from them have similar energies and cannot be separated in the PE spectrum.



25 26

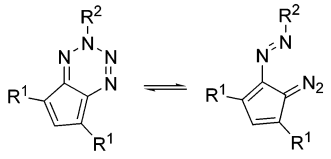
The PE spectrum of **26** was also recorded and interpreted by ab initio HF and Becke 3LYP calculations.[30] Attempts to assign ionization potentials of **25** and **26** to molecular orbitals obtained by semiempirical PM3 calculations indicate that this method is not suited for these molecules.

## *4. Ring-Chain Tautomerism*

2-Aryl-2*H*-cyclopenta[*e*]-1,2,3,4-tetrazines **6** exist in equilibrium with (arylazo)diazocyclopentadienes **7**, both tautomers being observed in the NMR spectra (see sections 3.2 and 3.3).[9] Some of them are listed in Table 8.

As the ratios indicate, the ring−chain equilibrium between **6** and **7** tautomers strongly depends on the nature of the $R^2$ group connected to the nitrogen atom. For $R^2$ = Ar, the electron-withdrawing substituents at the benzene ring, as well as ortho substituents, shift the equilibrium toward the open-chain structure **7**. The electron-releasing substituents in the para position produce an opposite effect. A buttressing effect of the bulky *tert*-butyl groups in the cyclopentadiene ring ($R^1$ = *t*-Bu) shifts the equilibrium in favor of the cyclic structure **6**. In contrast to the aryl-substituted species, 2-methyltetrazines ($R^2$ = Me) exist only in the cyclic form. A significant influence of electron-withdrawing substituents (Br, COH, $COCF_3$) in the 5- or 7-position of **6** on the azodiazo−tetrazino equilibrium has not been observed.

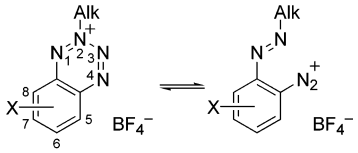
**Table 8. Ratio of the Tautomers 6 ⇆ 7 in $CDCl_3$ Solution**



6 7

| $R^1$ | $R^2$ | **6**:**7** |
|---|---|---|
| H | 4-$MeOC_6H_4$ | >98:<2 |
| H | Ph | 97:3 |
| H | 4-$NO_2C_6H_4$ | 87:13 |
| H | 2-$MeC_6H_4$ | 77:23 |
| H | 2-Me-4-$NO_2C_6H_3$ | 6:94 |
| H | 2,4-$(NO_2)_2C_6H_3$ | <2:>98 |
| *t*-Bu | Ph | >98:<2 |
| *t*-Bu | 4-$NO_2C_6H_4$ | 95:5 |
| *t*-Bu | 2,4-$(NO_2)_2C_6H_3$ | <2:>98 |
| H | Me | 100:0 |
| *t*-Bu | Me | 100:0 |

**Table 9. Ratio of Tautomers 8/9 at 298 K in Dependence of the Substituents X**

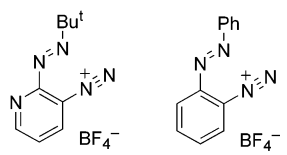


8 9

| compd | alk | X | **8**:**9** ratio (%) |
|---|---|---|---|
| **8a/9a** | *t*-Bu | H | 70:30 |
| **8b/9b** | *t*-Bu | 7-Br | 45:55 |
| **8c/9c** | *t*-Bu | 6-Br | 85:15 |
| **8d/9d** | *t*-Bu | 7-Me | 60:40 |
| **8e/9e** | *t*-Bu | 6-Me | 85:15 |
| **8f/9f** | *t*-Bu | 5,7-$Br_2$ | 100:0 |
| **8g/9g** | *t*-Bu | 5,7-$Cl_2$ | 100:0 |
| **8h/9h**[a] | Me | H | 70:30 |
| **8i/9i**[a] | Me | 5,7-$Br_2$ | 95:5 |

[a] **8h**/**9h** and **8i**/**9i** in $CD_3CN$; all others in acetone-$d_6$.

The phenyldiazonium salt **27** bearing an ortho phenylazo substituent has been known to exist in the open-chain form,[31] and the same is true for pyridinediazonium salt **23** with (*tert*-butyl)azo substituent.[10]

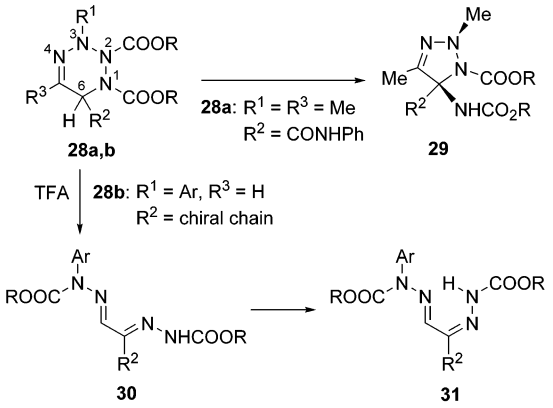


23 27

At the same time, the salts **9** bearing ortho alkylazo substituents exist in equilibrium with the 2-alkyl-1,2,3,4-benzotetrazinium salt cyclic isomers **8**. This equilibrium is fast on the NMR time scale, and only one set of signals is observed in the $^1$H and $^{13}$C NMR spectra (see section 3.2).

As Table 9 shows, the equilibrium strongly depends on the substituents at the benzene ring and is practically unaffected by the alkyl substituents (meth-

**Scheme 1**



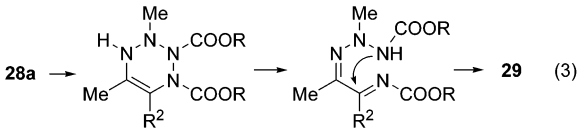

yl or *tert*-butyl) at the azo group. The equilibrium in the 5,7-dihalogen-substituted salt **8f**/**9f** and **8g**/**9g** is entirely shifted in favor of the cyclic form **8**, whereas for salts **8a**/**9a** bearing no substituents at the benzene ring, the cyclic form proportion is equal to 70%. On variation of temperature of the sample of **8a**/**9a** in acetone solution from 320 to 220 K, the percentage of the cyclic tautomer **8** increased from 49% to 93%.

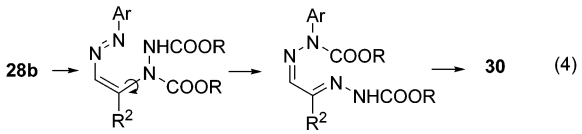
The rather weak stability of benzotetrzine 1-oxides (section 7.2) and hypothetical benzotetrzine 2-oxides (section 7.4.3) is due to their ability to turn into their unstable open-chain tautomers. In contrast, the increase in stability of benzotetrazine 1,3-dioxides is, in particular, due to the fact that the tetrazine 1,3-dioxide ring cannot take part in ring−chain tautomerism.

## 5. Reactivity of Tetrahydro Ring Systems

In 1991 the rearrangement of 1,2,4,6-tetrahydro-1,2,3,4-tetrazines **28a** was described.[32] It was accompanied by ring contraction to afford 2,5-dihydro-1*H*-1,2,3-triazoles **29** (Scheme 1). The reaction, which took place at room temperature, was strongly accelerated by addition of trifluoroacetic acid.

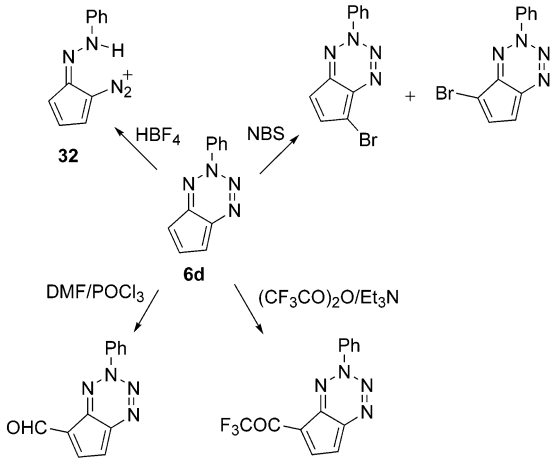
The rearrangement of **28a** could involve the proton transfer from C-6 carbon to N-4 nitrogen followed by cleavage of the N1−N2 bond and subsequent intramolecular nucleophilic addition[32,33] (eq 3).



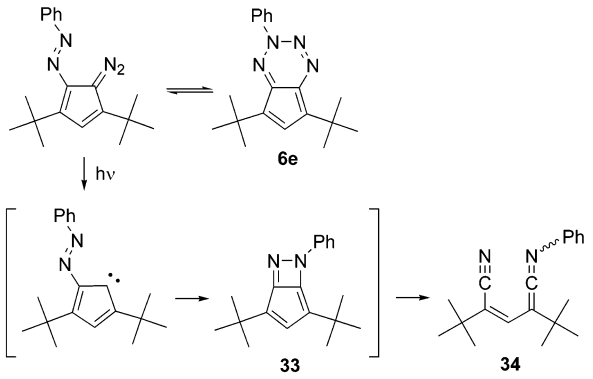




However, chiral tetrazines **28b** derived from carbohydrates, when treated with trifluoroacetic acid in organic solvent, did not afford five-membered heterocycles but rather gave glycosazone derivatives **30** and **31** with (1*E*,2*Z*)- and (1*E*,2*E*)-configurations, respectively, around the C=N bonds[33] (Scheme 1). This rearrangement should most likely involve cleavage of the N2−N3 bond followed by intramolecular attack of the azo group on the ester function linked with the N-1 atom to give osazone with (1*Z*,2*Z*)-configurations, which undergoes acid-catalyzed inversion to the thermodynamically more stable isomer **30** (eq 4). The distinctive features of tetrazines **28b** in comparison with **28a**, which are probably responsible for the changes in reactivity of the tetrazine ring, are the lower acidity of the hydrogen atom located at C-6 and the presence of an aryl substituent instead of methyl at N-3 of the tetrazine ring.

**Scheme 2**



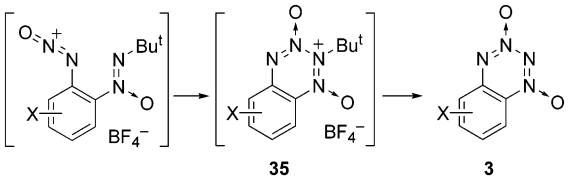

**Scheme 3**



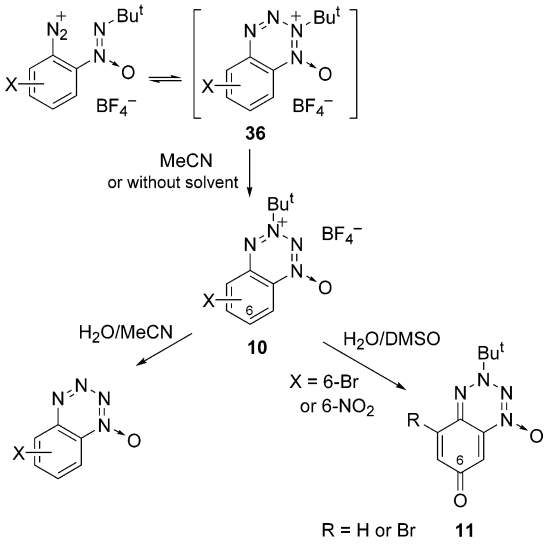

## 6. Reactivity of Cyclopenta-annulated Ring System

Treatment of the tetrazine **6d** containing 3% of the open-chain tautomer (see section 4) with $HBF_4$ resulted in ring opening to yield diazonium salt **32**. At the same time, the bromination with NBS, formylation under Vilsmeier conditions, and acylation with trifluoroacetic anhydride resulted in electrophilic substitution in the 5- or 7-positions. On the other hand, photolysis of the equilibrium mixture of **6**/**7** is dominated by the reactivity of the diazo group of the ring-opened structure. For example, irradiation of a solution of **6e** with a mercury vapor lamp afforded the ketene imine **34**. The reaction starts presumably with a loss of the $N_2$ molecule followed by formation of bicyclic intermediate **33**, which finally is transformed into the ketene imine by formal [2 + 2]cycloreversion.

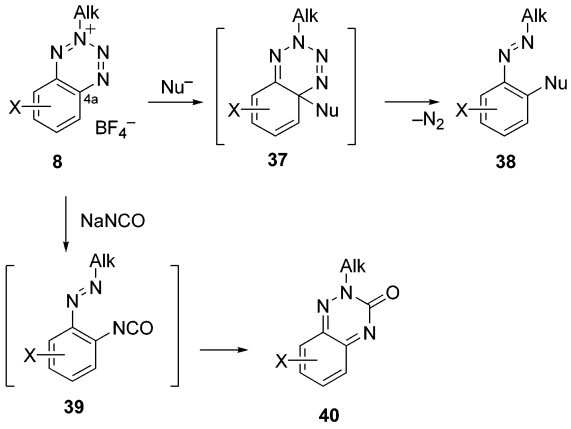
**Scheme 4**



**Scheme 5**



**Scheme 6**



## 7. Reactivity of Fully Conjugated Ring Systems

### 7.1. Reactivity of Tetrazinium Salts

The 2-(*tert*-butyl)tetrazinium 1,3-dioxide tetrafluoroborates **35** (Scheme 4) as well as the 2-(*tert*-butyl)-tetrazinium 1-oxide tetrafluoroborates **36** (Scheme 5) were postulated as intermediates in the intramolecular reaction of the oxo diazonium ion[26] and diazonium ion,[12] respectively, with the *tert*-butyl-*NNO*-azoxy group. Both salts are short-living species, and one never observes them during in situ $^1$H NMR monitoring of the reaction.

The tetrazinium 1,3-dioxide salts **35** easily eliminated the *tert*-butyl cation, resulting in benzotetrazine 1,3-dioxides **3** (see section 8.3).

The salts **36** rearranged to give more thermodynamically stable 2-(*tert*-butyl)-tetrazinium 4-oxide salts **10**. The rearrangement involves the *N*,*N*-[1,2]-migration of the *tert*-butyl group, the mechanism of which is not quite clear. It could involve a simultaneous process with a three-center transition state as well as an elimination−addition mechanism involving a tight ionic pair. The argument in support of the former mechanism is the fact that the rearrangement takes place not only in solution but also in the solid state.

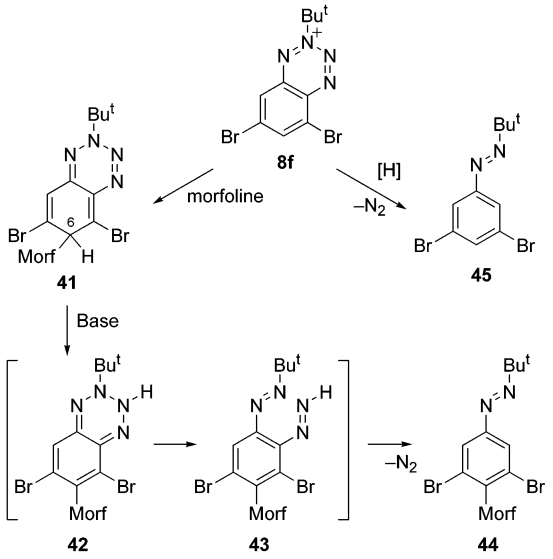
The stability of salts **10** strongly depends on the substituents on the benzene ring. In general terms, electron-withdrawing substituents facilitate elimination of the *tert*-butyl cation and electron-releasing ones retard it. For example, salt **10** bearing the bromine substituent at the 6-position is quite stable at room temperature in the solid state (mp 129−133 °C dec), and the salt **10** bearing the nitro group at the same position is too unstable to be isolated even at 0 °C. In MeCN containing a small amount of $H_2O$, salts **10** eliminated the *tert*-butyl cation to afford benzotetrazine 1-oxides (see section 8.3). However, when salts **10** bearing the nitro group or bromine atom at the 6-position were treated with DMSO solution containing a small amount of water, displacement of the nucleoufugal groups at that position took place to afford the quinoid structures **11**. They are quite stable compounds (R = H, mp 188−189 °C, dec) that are red in color. The chemistry of this new type of tetrazine derivatives has not been studied yet.

The reactivity of 2-alkylbenzotetrazinium salts **8a,f,h,i** (Table 9) dramatically differs from that of their *N*-oxides[34] (Scheme 6). The *tert*-butyl cation is not eliminated, and thus, the parent benzotetrazine **3a** cannot be obtained by this way. *O*-Nucleophiles and halogenide and cyanide ions ($H_2O$, MeONa, AcONa, NaCN, NaCl, $Bu_4NF$) attack the 4a-position of salts **8** to afford azo compounds **38** via the postulated intermediate **37**, which loses the $N_2$ molecule. Treatment with NaNCO affords 1,2,4-benzotriazinones **40**, which are more thermodynamically stable then the open-chain tautomers **39**. All of these reactions proceed at room temperature in high yields even with salt **8a** containing 70% of the cyclic isomer in the equilibrium mixture.

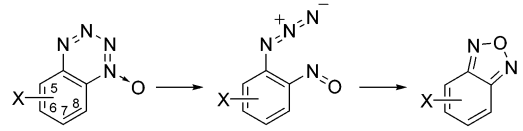
The reaction of salts **8** with amines depends on the nature of the amine and on the percentage of the cyclic form in the equilibrium mixture. Salt **8a/9a** (70% of the cyclic form) reacts with morpholine in the open-chain form as an ordinary diazonium salt to afford the appropriate triazene. Salt **8f** (100% of the cyclic form) reacted with a number of amines ($Pr_2NH$, $PhNH_2$, 4-$ClC_6H_4NH_2$) with the evolution of $N_2$ molecule to give azo compounds **38** (Scheme 6). However, morpholine attacks this salt at the 6-position to afford intermediate **41**, the structure of which was confirmed by NMR spectroscopy (Scheme 7).

Treatment of **41** with a base (or excess morpholine) gives rise to azo compound **44**. This reaction can be rationalized by proton migration to give intermediate **42** followed by ring opening to afford azo compound **43**. The latter could easily lose the $N_2$ molecule to give **44**. Reduction of salts **8** with aminobenzenes bearing electron-releasing substituents (e.g., with anisidine) resulted in azo compounds **45** (Scheme 7). This reaction could proceed via the intermediate related to **43**.

**Scheme 7**




**Scheme 8**




## 7.2. Thermal Stability of Benzotetrazine 1-Oxides (BTOs) and Benzotetrazine 1,3-Dioxides (BTDOs)

The pronounced cyclic conjugation in the 1,2,3,4-tetrazine 1-oxide ring of benzotetrazine 1-oxides (BTOs) **46** revealed by the X-ray studies[35] does not markedly stabilize the molecule. The irreversible opening of the ring results in open-chain tautomer *o*-azidonitrosobenzenes **47** (Scheme 8).[12] The latter cyclize with the evolution of nitrogen to afford benzofurazans. In some cases *o*-azidonitrosobenzenes were isolated.

The thermal stability of BTOs depends on the electronic and steric effects of the ring substituents. The most stable are compounds bearing a $R_2N$ group in the 7-position. The bromine atom in the 5-position also stabilizes the molecule, probably owing to a buttressing effect. For example, 5-Br-7-$NMe_2$−BTO can be stored for 1 week at room temperature without distinct decomposition. At the same time, BTOs bearing the nitro groups in the 5- or 7-position are too unstable to be isolated.

Most benzotetrazine 1,3-dioxides (BTDOs) **3** obtained are quite stable compounds, melting in the 170−250 °C region. As a rule, they did not decompose below 200 °C. Only two representatives of the phenanthrene-like system with two 1,2,3,4-tetrazine 1,3-dioxide rings were synthesized. The 6-chloro-substituted derivative **12a** (see the Introduction) melts at 140 °C with decomposition, and 6-MeNH-substituted compound **12b** decomposes without melting above 210 °C.[13] The furazano-annulated 1,2,3,4-tetrazine 1,3-dioxide **4** (see the Introduction) is not as stable. It melts with decomposition at 112 °C.[4] However, it is more stable than triazolo-annulated 1,2,3,4-tetrazine **5** (see the Introduction), which slowly decomposes at room temperature.[5]

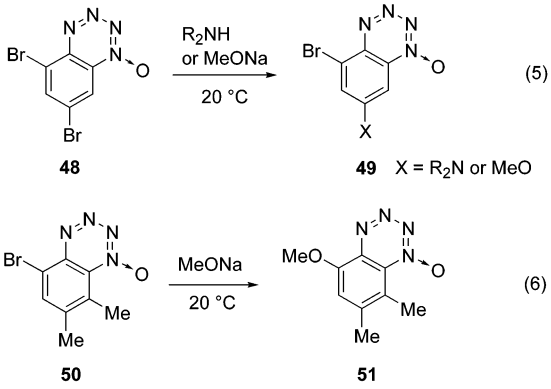
The rather high stability of the 1,2,3,4-tetrazine 1,3-dioxide ring is due, in particular, to an influence of the two oxygen atoms, located in the 1- and 3-positions, which determine the transformation pathways of the nitrogen-containing ring. In fact, the 1,3-arrangement of oxygen atoms should be the most favorable relative to any other hypothetical case. On one hand, 1,2,3,4-tetrazine 1,3-dioxide, unlike tetrazine itself, tetrazine 1-oxide, tetrazine 2-oxide, and tetrazine 2,3-dioxide, cannot take part in ring−chain tautomerism with formation of unstable or highly reactive open-chain tautomers. On the other hand, 1,2,3,4-tetrazine 1,3-dioxide cannot lose a thermodynamically very stable $N_2$ molecule, again in contrast to tetrazine or tetrazine 1,4-dioxide. The loss of $N_2O$ is not as favorable as the loss of $N_2$.

Zwitterionic spiro-*σ*-complexes **13a** (mp 200−205 °C dec) and **13b** (mp 210−220 °C dec) (see the Introduction), in which the negative charges are distributed over the tetrazine 1,3-dioxide system, are also quite stable.[14] The anionic tetrazine 1,3-dioxide fragment of this system is similar to the rather stable anion of dinitroamidic acid.[36]

## 7.3. Reactivity of Benzotetrazine 1-Oxides (BTOs)

Study of the reactivity of benzotetrazine 1-oxides (BTOs) was confined within the nucleophilic displacement reactions.[12] Treatment of 5,7-$Br_2$−BTO **48** with nucleophiles (secondary amine or MeONa/MeOH) resulted in displacement of the bromine in the 7-position to yield BTOs **49** (eq 5).

BTO **51** resulted from displacement of the bromine atom by the methoxide ion in the 5-position of **50** (eq 6).




In the case of 5,6,7-$Br_3$−BTO **52**, competitive displacement in the 6- and 7-positions took place. BTO **53** and *o*-azidonitrosobenzene **55** were isolated in a 3:2 ratio. The intermediate BTO **54** proved to be unstable at room temperature.

## 7.4. Reactivity of Benzotetrazine 1,3-Dioxides (BTDOs)

The electrophilic[37] and nucleophilic[38] displacement reactions of benzotetrazine 1,3-dioxides (BTDOs) were studied rather comprehensively. The reduction of BTDOs was also studied.[39]

**Scheme 9**

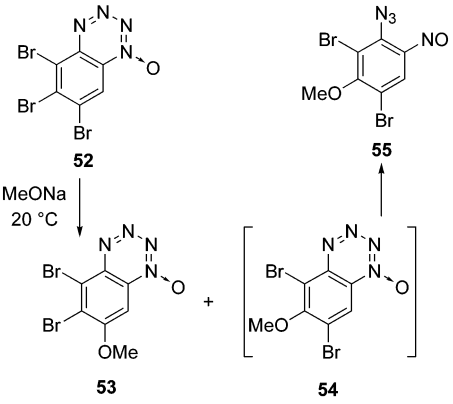
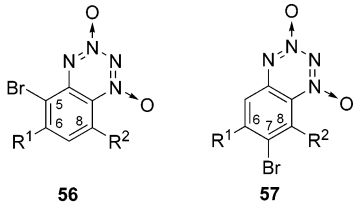



**Table 10. Ratio of the Isomers 56/57 Resulting from Monobromination of BTDOs**

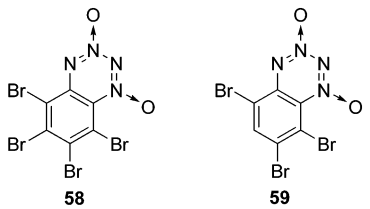



| $R^1$ | $R^2$ | ratio of isomers **56**:**57** |
|---|---|---|
| H | H | 47:53 |
| Br | H | 50:50 |
| H | Br | 87:13 |
| Br | Br | 100:0 |

### *7.4.1. Electrophilic Displacement*

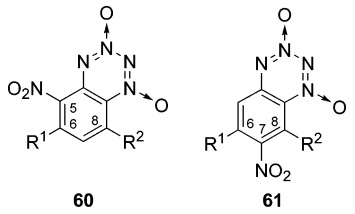
**7.4.1.1. Bromination.** Treatment of BTDOs with dibromoisocyanuric acid (DBI) in $CF_3COOH$ containing $H_2SO_4$ (15−20%) allowed insertion of one bromine atom in the ring at the 5- or 7-position to afford a mixture of isomers **56** and **57**.[37] Bromination of the parent BTDO **3a** and 6-Br−BTDO gave a nearly equal ratio of isomers (Table 10). 8-Br−BTDO was brominated mainly at the 5-position. Bromination of 6,8-dibromo-BTDO proceeded exclusively at the 5-position.

Under more drastic conditions (DBI/$H_2SO_4$), several bromine atoms were introduced into the BTDOs in one step. Thus, tetrabromo derivative **58** was obtained from 6,8-dibromo-BTDO. Bromination of parent BTDO **3a** under these reaction conditions resulted in insertion of three bromines to afford BTDO **59**, containing bromine atoms in positions 5, 7, and 8.

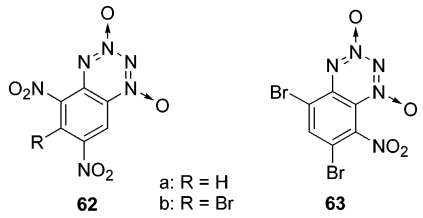



**7.4.1.2. Nitration.** The 1,2,3,4-tetrazine 1,3-dioxide system in benzo-annulated derivatives is inert to strong acids and oxidants (e.g., oleum). Treatment of BTDOs with a $HNO_3/H_2SO_4$ mixture at room temperature resulted in 5-nitro and 7-nitro isomers **60** and **61** (Table 11).[37] The **60**/**61** isomer ratio depends on the substituents in the 6- and 8-positions. In the case of nitration of the parent BTDO **3a**, the 7-nitro isomer is predominant. The substituent (Br, MeO, $Me_2N$) in the 6-position moves the ratio in favor of 5-$NO_2$-isomer **60**. In the case of 6-$Me_2N$−BTDO, the 7-nitro isomer was not observed at all. The substituent (Br) in the 8-position unexpectedly moves the ratio in favor of 7-$NO_2$-isomer **61**, the rate of the reaction being slightly increased. Nitration of the parent BTDO **3a** and 6-Br−BTDO in more drastic reaction conditions ($HNO_3$/(20% oleum), 90 °C) resulted in 5,7-dinitro derivatives **62a**[25,37] and **62b**,[14] respectively.

**Table 11. Ratio of the Nitro Isomers 60/61 Resulting from Nitration of BTDOs**




| $R^1$ | $R^2$ | ratio of isomers **60**:**61** |
|---|---|---|
| H | H | 33:67 |
| Br | H | 90:10 |
| MeO | H | 99:1 |
| $NMe_2$ | H | 100: 0 |
| H | Br | 19:81 |

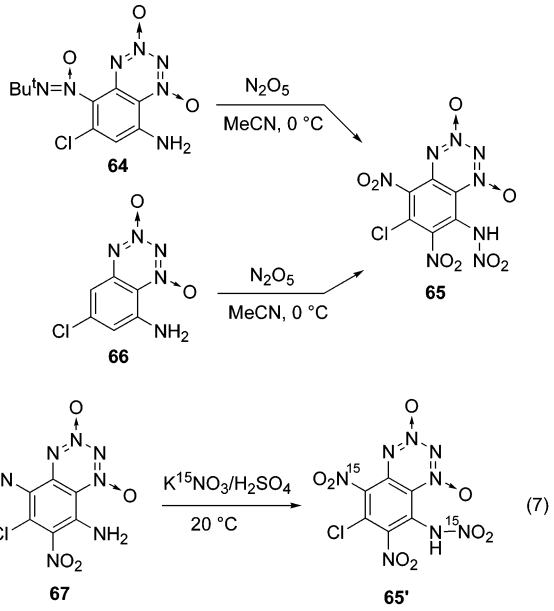



When the 5- and 7-positions are occupied with bromine atoms, the nitration ($HNO_3$/oleum) proceeded exclusively in the 8-position to give BTDO **63**.

Thus, nitration and bromination rates at different positions of the BTDO changes in the following order 5 ≈ 7 ≫ 8 > 6, though bromination is usually less selective when there is a choice between positions 5 and 7.

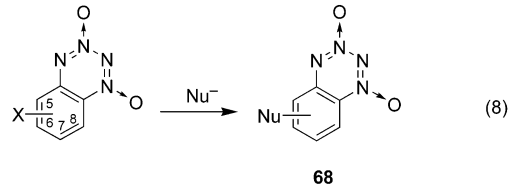
Unexpected electrophilic displacement of the *tert*-butyl-*NNO*-azoxy group by the nitro group took place when BTDO **64** was treated with $N_2O_5$.[13] This process is facilitated by the amino group in the para position. The readiness of this displacement imposes particular limitations on the possibility of annulation of BTDOs with the second 1,2,3,4-tetrazine 1,3-dioxide ring (see section 8.3). The structure of the displacement product **65** was confirmed by direct nitration of BTDO **66**. Exchange of the nitro groups in BTDO **67** in the nitrating conditions is of a related mechanism. This exchange was observed when BTDO **67** was treated with $^{15}N$-labeled $KNO_3$ in $H_2SO_4$ to give BTDO **65′**.[13]

**Scheme 10**




### 7.4.2. Nucleophilic Displacement

Treatment of monosubstituted BTDOs (X = 6-Br, 7-Br, 8-Br, 7-$NO_2$) with nucleophiles (KOH/MeOH, $NaN_3$/DMFA, $Me_2NH$/DMFA, $MeNH_2$/DMSO) at room temperature resulted in substitution of the nucleofugal groups to afford BTDOs **68** in good to excellent yields with the exception of the reaction of 7-$NO_2$−BTDO with $MeNH_2$, which gave a mixture containing no expected product.[38]




Treatment of dibromo-BTDOs with KOH/MeOH afforded mixtures of isomers (Table 12). All the above experiments show that the reactivity of the BTDO positions with respect to nucleophilic substitution changes in the following order: 6 ≈ 8 > 7 > 5.

However, treatment of 6,8-$Cl_2$−BTDO with ammonia in DMSO solution resulted predominantly in 8-substituted isomer 8-$NH_2$-6-Cl−BTDO (Table 13), evidently due to intramolecular interaction of the amino group with the *N*-oxide atom in the intermediate *σ*-complex.[13] 5-(*tert*-Butyl-*NNO*-azoxy)-6,8-$Cl_2$−BTDO in the same reaction conditions afforded nearly equal amounts of 6- and 8-amino isomers (Table 13).

5,7-$(MeO)_2$−BTDO and 6,7-$(MeO)_2$−BTDO resulted from the reaction of 5,7-$Br_2$−BTDO and 6,7-$Br_2$−BTDO, respectively, with excess MeOH/KOH.[38]

Bipolar spiro-*σ*-complexes **13a** and **13b** (see the Introduction) resulted from the reaction of 6-bromo-5,7-dinitro-BTDO with 2-(*N*-benzylamino)tropone and with thallium salt of 3,5,7-trimethyltropolone, respectively.[14]

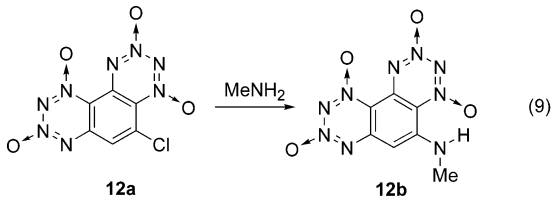
**Table 12. Reaction of Dibromo-BTDOs with KOH/MeOH**

| substituents in starting BTDOs | substituents in resultant BTDOs (isomer ratio in parentheses) |
|---|---|
| 5,7-$Br_2$ | 5-Br-7-MeO/7-Br-5-MeO (90:10) |
| 6,7-$Br_2$ | 6-Br-7-MeO/7-Br-6-MeO (2:98) |
| 6,8-$Br_2$ | 6-Br-8-MeO/8-Br-6-MeO (38:62) |

**Table 13. Reaction of Dichloro-BTDOs with $NH_3$/DMSO**

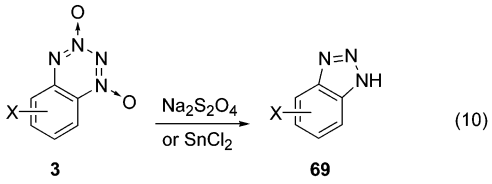
| substituents in starting BTDOs | substituents in resultant BTDOs (isomer ratio in parentheses) |
|---|---|
| 6,8-$Cl_2$ | 6-$NH_2$-8-Cl/8-$NH_2$-6-Cl (14:86) |
| 5-(*t*-Bu-azoxy)-6,8-$Cl_2$ | 6-$NH_2$-5-(*t*-Bu-azoxy)-8-Cl/8-$NH_2$-5-(*t*-Bu-azoxy)-6-Cl (46:54) |

The chlorine in the 6-position of **12a** was readily replaced by methylamine to afford **12b** (eq 9).[13]




### 7.4.3. Reduction

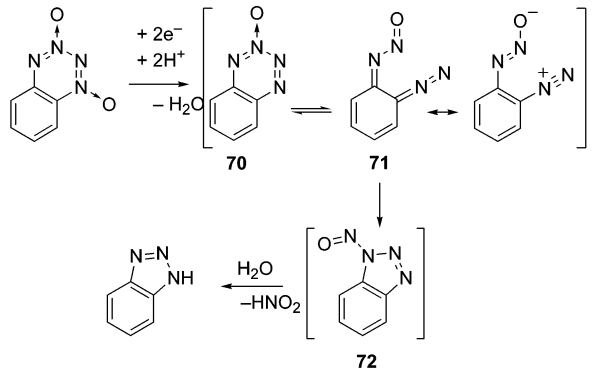
Reduction of the parent BTDO **3a**, 7-$NO_2$−BTDO, and 5,7-$Br_2$−BTDO with $Na_2S_2O_4$ or $SnCl_2$ afforded benzotriazoles **69** (eq 10).[39]



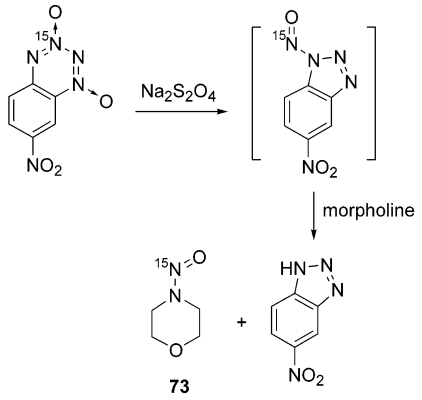

The reduction was suggested to proceed via intermediate benzotetrazine 2-oxides **70** (Scheme 11). The latter could provide the open-chain tautomer **71**, which could irreversibly cyclize into thermodynamically more favorable *N*-nitrosobenzotriazole **72**. The following hydrolysis could provide benzotriazole and nitrous acid.

This sequence of transformations was confirmed by $^{15}N$-labeling experiments (Scheme 12), which showed that the N-3 atom of the tetrazine ring is finally incorporated into the nitroso group of *N*-nitrosomor-

**Scheme 11**



**Scheme 12**

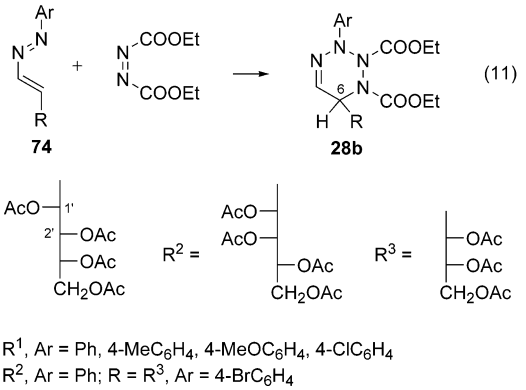



pholine **73** when morpholine was used as a trap for nitrosating species.

## *8. Ring Synthesis*

### 8.1. Synthesis of Tetrahydro Ring Systems

The (6*R*)- and (6*S*)-diastereomers of functionalized 1,2,3,6-tetrahydro-1,2,3,4-tetrazines **28b** resulted from the stereoselective Diels−Alder reactions of chiral 1,2-diaza-1,3-butadienes **74**, derived from acyclic carbohydrates, with diethyl azodicarboxylate (eq 11).[33] Reactions proceed slowly in benzene solutions at room temperature but are greatly accelerated by microwave irradiation.

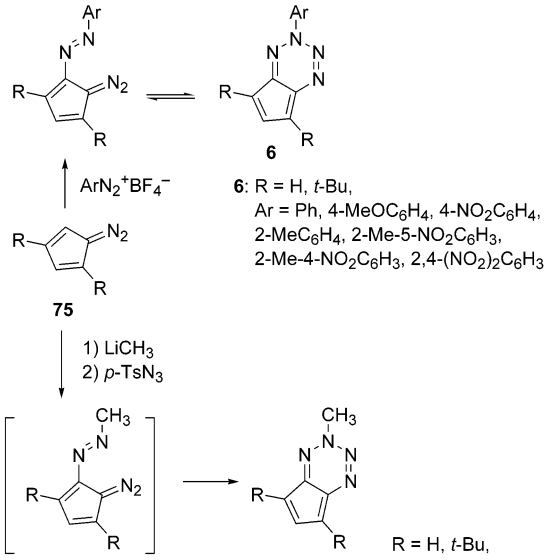



The observed stereoselectivity of **28b** is markedly dependent on the relative stereochemistry of the chiral substituent R at C-1′,2′. Thus, 1,2-diazoalkenes derived from per-*O*-acylated sugars, having a threo configuration at C-1′,2′, afford tetrazines with high facial selectivity (for R = $R^1$, Ar = 4-$CH_3C_6H_4$ the diastereomeric ratio is 88:12), whereas those having an erythro configuration at C-1′,2′ give products with lower diastereomeric ratios. The facial diastereoselection has been rationalized by a PM3 computational study.

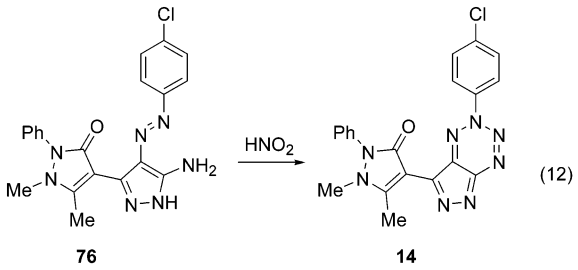
### 8.2. Synthesis of Dihydro Ring Systems

Cyclopenta-annulated 2-aryltetrazines **6** existing in equilibrium with their open-chain isomers (see section 4) resulted from the coupling of the diazocyclopentadienes **75** with arenediazonium salts.[9] Cyclopenta-annulated 2-methyltetrazines were obtained by addition of methyllithium to **75** followed by a diazo

**Scheme 13**




transfer reaction using tosyl azide. The intermediate open-chain isomers were not observed in the latter case. Diazotization of 5-amino-4-arylazopyrazole **76** afforded 2*H*-pyrazolo[3,4-*e*][1,2,3,4]tetrazine **14**[15] (eq 12). This compound represents a new annulated tetrazine ring system, related to 2,6-dihydro-7*H*-pyrazolo[3,4-*e*][1,2,3,4]tetrazine-7-ones[40] (see the Introduction). Unfortunately, the spectral characterization of **14** is not very exhaustive, and only IR and $^1$H NMR spectra are available. Nevertheless, its cyclic structure is confirmed by the fact that this compound does not take part in coupling reactions, typical of diazonium salts.

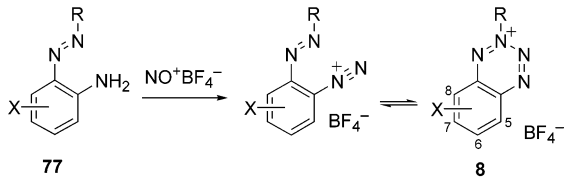



For the synthesis of quinoid compounds **11** by nucleophilic displacement in benzotetrazinium salts, see Scheme 5.

### 8.3. Synthesis of Fully Unsaturated Rings

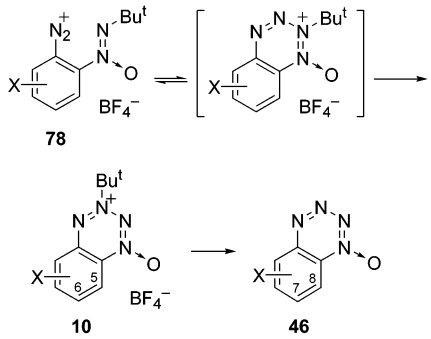
2-Alkylbenzotetrazinium salts **8**, existing in equilibrium with their open-chain isomers (see section 4), resulted from the diazotization of the azo anilines **77** with nitrosonium tetrafluoroborate.[10] 2-(*tert*-Butyl)-benzotetrazinium 4-oxides **10** resulted from intramolecular cyclization, involving the *tert*-butyl-*NNO*-azoxy group and diazonium ion followed by *N*,*N*-[1,2]-shift of the *tert*-butyl group (see section 7.1). Further elimination of the *tert*-butyl cation afforded the benzotetrazine 1-oxides **46**. The feasibility of the isolation of both **10** and **46** depends on the relative rates of generation and on further decomposition (see section 7.2). Diazonium salt **78** without substituents at the benzene ring began to cyclize only at temper-

**Scheme 14**

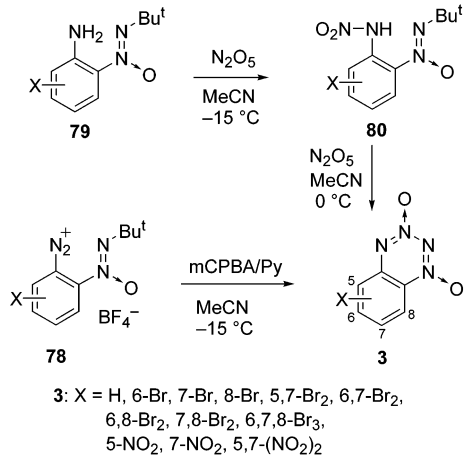


R = Me, X = H, 5,7-$Br_2$
R = *t*-Bu, X = H, 7-Br, 6-Br, 7-Me, 6-Me, 5,7-$Br_2$, 5,7-$Cl_2$

**Scheme 15**



**Scheme 16**



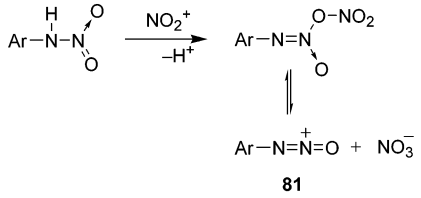
**3**: X = H, 6-Br, 7-Br, 8-Br, 5,7-$Br_2$, 6,7-$Br_2$, 6,8-$Br_2$, 7,8-$Br_2$, 6,7,8-$Br_3$, 5-$NO_2$, 7-$NO_2$, 5,7-$(NO_2)_2$

atures above 50 °C. This temperature was too high to isolate **10** and **46**. The strong electron-withdrawing substituent, e.g., the nitro group in the para position to the diazonium group, makes the cyclization proceed easily even at 0 °C. However, both **10** and **46** bearing a nitro substituent are unstable. Thus, this method can be used for the synthesis of compounds with a limited set of substituents (for salts **10**: 6-Br, 6,8-$Br_2$, 6,7-$Br_2$, 6-Br-7-Me, 6,7,8-$Br_3$, 6,8-$Br_2$-7-Me, yield 30−85%; for BTO **46**: 7-Br, 6,7-$Br_2$, 5,7-$Br_2$, 5,6,7-$Br_2$, 5-Br-6,7-$Me_2$, yield 15−50%). At the same time, the benzotetrazine 1-oxides with electron-releasing substituents, which in some cases are rather stable, were obtained by nucleophilic displacement of bromine in bromo-BTOs (section 7.3).

A synthetic pathway to benzotetrazine 1,3-dioxides (BTDOs) **3** involves treatment of azoxy anilines **79** with nitrating agents (e.g., $N_2O_5$ or $NO_2BF_4$) in organic solvent[25,26,37,38] (Scheme 16).

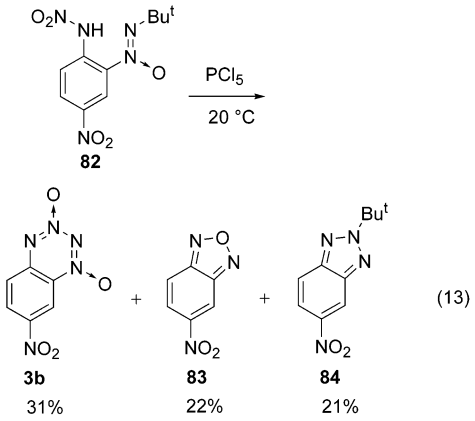
In the first stage of this reaction, *N*-nitroanilines **80** were formed, which were suggested to afford the oxodiazonium ion **81** via *O*-nitration of the nitramine followed by ionic dissociation (Scheme 17).[4,25,26]

**Scheme 17**



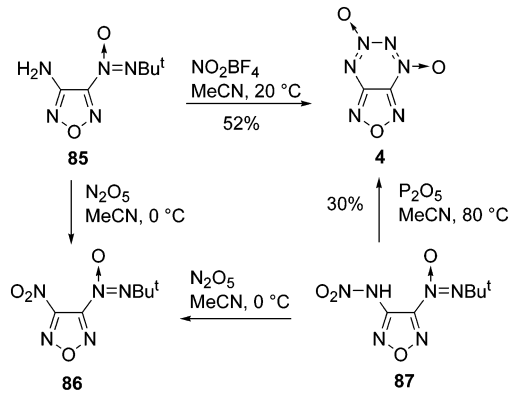
The tetrazine ring formation was rationalized as an electrophilic attack of the oxodiazonium ion on the *tert*-butyl-*NNO*-azoxy group, followed by elimination of the *tert*-butyl cation (see section 7.1, Scheme 4).

The BTDOs **3** (X = H or 7-$NO_2$) were also formed in good yields when the appropriate *N*-nitroanilines **80** were treated with phosphoric anhydride in $CH_3$-CN at room temperature.[41] This reaction was also suggested to proceed via oxodiazonium ion **81**. With phosphorus pentachloride, the reaction pathway depends on the ring substituents. Whereas *N*-nitroaniline **80** with X = H gave an 87% yield of BTDO **3a** when treated with this reagent, *p*-nitro-substituted *N*-nitroaniline **82** yielded 31% of the 7-$NO_2$− BTDO **3b** along with benzofurazan **83** and 2-(*tert*-butyl)benzotriazole **84** (eq 13). The mechanism of formation of the two latter compounds is not clear as yet, taking into account that **3b** is resistant to $PCl_5$ in the reaction conditions and cannot serve as a precursor of benzofurazan **83**.

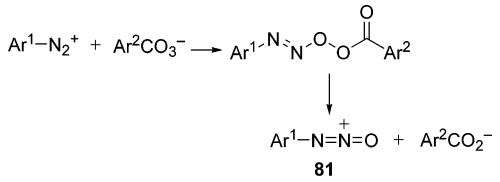


Treatment of 3-amino-4-(*tert*-butyl)azoxyfurazan **85** with $NO_2BF_4$ gave furazano-annulated tetrazine 1,3-dioxide **4**.[4] This cycle was obtained also by treatment of the *N*-nitroamine **87** with $P_4O_{10}$. Treatment of **85** or **87** with $N_2O_5$ resulted in oxidation of the amino group to the nitro group to give **86** rather than in cyclization into **4**.[42] The oxidation is suggested to proceed also via oxodiazonium ion **81**. Attack of the terminal nitrogen of **81** by the $NO_{3-}$ anion could result in formation of the nitroso group, followed by oxidation of the latter with the excess $N_2O_5$ to the nitro group. One more synthetic route to BTDOs **3** involves treatment of diazonium salts **78** with *m*-chloroperbenzoic acid in the presence of pyridine as a base (Scheme 16).[3,26] The diazonium salts were generated in situ by treatment of the appropriate azoxy anilines with $NOBF_4$ at −15 °C. The reaction was rationalized by a mechanism involving the coupling of the diazonium ion with the anion of peracid followed by ionic dissociation facilitated by

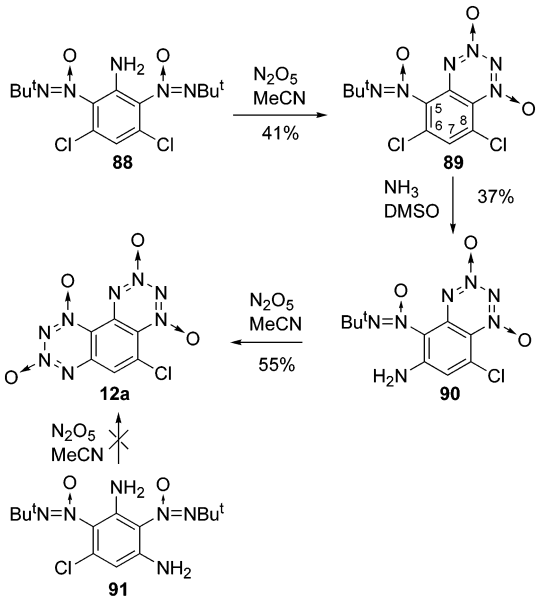
**Scheme 18**



**Scheme 19**



**Scheme 20**



intramolecular solvatation of the oxodiazonium ion **81** by the neighboring azoxy group (Scheme 19).

The yields of BTDOs obtained by this method are similar to those obtained by the nitration method. It should be noted that BTDOs did not result from the oxidation of benzotetrazine 1-oxides by mCPBA.

The novel heterocyclic system **12**, in which the benzene ring is annulated with two 1,2,3,4-tetrazine 1,3-dioxide rings, was synthesized by the three-step sequence starting from bis-azoxy aniline **88**.[13] Treatment of the latter with $N_2O_5$ resulted in the first 1,2,3,4-tetrazine 1,3-dioxide ring formation. The following displacement of the chlorine atom at the 6-position of BTDO **89** with ammonia and subsequent repeated treatment with $N_2O_5$ resulted in the second 1,2,3,4-tetrazine 1,3-dioxide ring formation. However, this synthetic approach is difficult to perform on a large scale because 6-amino-substituted BTDO **90** can be separated from its 8-amino-substituted isomer (see Table 13) only by chromatography. A one-step synthetic route to system **12** involving the treatment of diamine **91** with $N_2O_5$ failed, probably owing to the displacement of one of the azoxy groups in the course of the reaction with $N_2O_5$.

## 9. Applications

Benzotetrazine 1,3-dioxides (BTDOs) showed biological activities, probably due to their ability to release nitrosating species in the course of reduction[39] (see section 7.4.3). Thus, they were considered as a new class of nitric oxide donors.[43] 5-Nitro- and especially 7-nitro-BTDOs are effective thiol-dependent activators of soluble guanylate cyclase.[44] They showed hypotensive activity and reduce the activity of caspase-3.[34]

The parent BDTO **3a** and its 6- and 7-bromo and 6,7-dibromo derivatives are inhibitors of ADP-induced aggregation of human platelets. They also show antimetastatic properties.[45]

The 6- and 7-bromo-BTDOs irreversibly and selectively inhibit activity of H,K-adenosinetriphosphatase in a microsomal fraction of stomach mucosa.[46]

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