Transannular Cyclizations of 1,2-Dithia-5,8-diazacyclodeca-4,8-dienes during Borohydride Reduction

Alummoottil V. Joshua,*‡ John R. Scott,† Sham M. Sondhi,‡ Richard G. Ball,‡ and J. William Lown*‡

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, T6G 2N8, Canada, and Department of Chemistry, University of Alberta, Edmonton, AB, T6G 2G2, Canada

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Reduction of certain 6-substituted 1,2-dithia-5,8-diazacyclodeca-4,8-dienes with sodium borohydride in ethanol at 25 °C affords as the major products isomeric 7- and 8-substituted imidazolidino[1,2-*d*]dithiazepines (the 8-product predominates) in addition to smaller amounts of the corresponding 1,2-dithia-5,8-diazacyclodecane. This result contrasts with literature reports that the 10-membered ring structure is the only isolable product of this reaction. Raising the temperature of the reaction to 50 °C has little effect on the product distribution, but at 0 °C the reaction affords 94.5% of the bicyclic imidazolidines. The regioselectivity of the reaction is rationalized by initial preferential reduction at the less hindered C=N bond of the 1,2-dithia-5,8-diazacyclodeca-4,8-diene followed by transannular cyclization to the isomeric bicyclic imidazolidines. The structures and conformations of the latter were secured in two cases by single-crystal X-ray diffraction analysis. The products were further characterized in these and other cases by preparation of N- and O-acyl derivatives and a cyclic carbamate. The imidazolidino[1,2-*d*]dithiazepines undergo slow further reduction (via the intermediate 1,2-dithia-5,8-diazacyclodec-4-ene) to the 1,2-dithia-5,8-diazacyclodecane.

Introduction

Recently a number of 1,2-dithia-5,8-diazacyclodecanes have been synthesized and labeled with Tc-99m under reducing conditions. The resulting complexes were evaluated as potential brain perfusion imaging agents by single photon emission computerized tomography (SPECT).[1-4] These ring systems, which can be reduced to bis(aminoethanethiols), form neutral lipid soluble oxotechnetium complexes capable of crossing the blood brain barrier. Several such complexes that show high initial brain uptake and fast wash-out have been reported.[1-3] Their principal clinical limitation is that the retention time is often not long enough for data collection in SPECT imaging. SPECT systems currently in use require 15 min to 1 h imaging time. Thus brain imaging agents that show both a high initial brain uptake and longer retention are essential for measuring local cerebral blood flow. Despite these limitations structures of this general type therefore appeared to offer advantages, both for the development of mono- and diamino derivatives to attempt to increase brain retention[5-10] and also as alternative metal sequestering agents for further development of our functional bleomycin agents.[11-13]

The 1,2-dithia-5,8-diazacyclodecanes have been reported[1-3] as being prepared by condensing a suitable dithiadialdehyde with an ethylenediamine and reducing the resulting bis(imine) with sodium borohydride. In our hands, although the desired products were obtained in low yields, the major products in all cases were bicyclic imidazolidines.

We report herein a detailed study of this borohydride-induced cyclization reaction with a view to establishing the generality of this process, the effects of substituents in the precursor on the regiochemistry of ring closure or subsequent reactions, the mechanism of the reductive cyclization, and the mechanism of reduction of bicyclic imidazolidines and dithiadiazacyclodecadienes to dithiadiazacyclodecanes in general.

Reductive Cyclization of 1,2-Dithia-5,8-diazacyclodeca-4,8-dienes to Imidazolidino[1,2-*d*]dithiazepines. The 1,2-dithia-5,8-diazacyclodeca-4,8-dienes 1 (Scheme I) were prepared by condensation of either 2,2′-dithiobis(2-methylpropanal)[1] or 2,2′-dithiobis(2-ethylbutanal)[1] with the appropriate substituted ethylenediamine.

In all of the cases examined the major products formed from the treatment of the 1,2-dithia-5,8-diazacyclodeca-4,8-dienes with 5 molar equiv of sodium borohydride in ethanol at 25 °C for 24 h are the imidazolidino[1,2-*d*]dithiazepines **3** (which represents a novel ring system) and not the 10-membered ring-saturated products **4** previously reported.[14] The structures of the major products were established by their characteristic spectral properties and unambiguously in selected cases by X-ray diffraction analysis (see below).

† Faculty of Pharmacy and Pharmaceutical Sciences.
‡ Department of Chemistry.

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(14) Sodium borohydride reduction of **1c** has been reported to yield **4c** in 91% yield together with an unidentified isomer of **4** in 6% yield (ref 3). The CIMS of our major product **3Bc** in this reaction shows m/z 263 (100, $M^+ + 1$), 264 (16.9, $M^+ + 2$), 265 (11.4, $M^+ + 3$). The peaks at $M^+ + 2$ and $M^+ + 3$ arise due to S isotopes. It appears likely that Kung et al. mistook the m/z = 265 of **3** for the $M^+ + 1$ peak of **4**. Compounds **3Ac** and **4** also exhibit $M^+ + 1$, $M^+ + 2$, and $M^+ + 3$ peaks. Similarly the physical data on reduction product from 3,3,6,6,10,10-hexamethyl-1,2-dithia-5,8-diazacyclodeca-4,8-diene are consistent with a major product of 1,1,4,4,7,7-hexamethylimidazolidino[1,2-*d*]dithiazepine rather than the 3,3,6,6,10,10-hexamethyl-1,2-dithia-5,8-diazacyclodecane previously assigned.[4]

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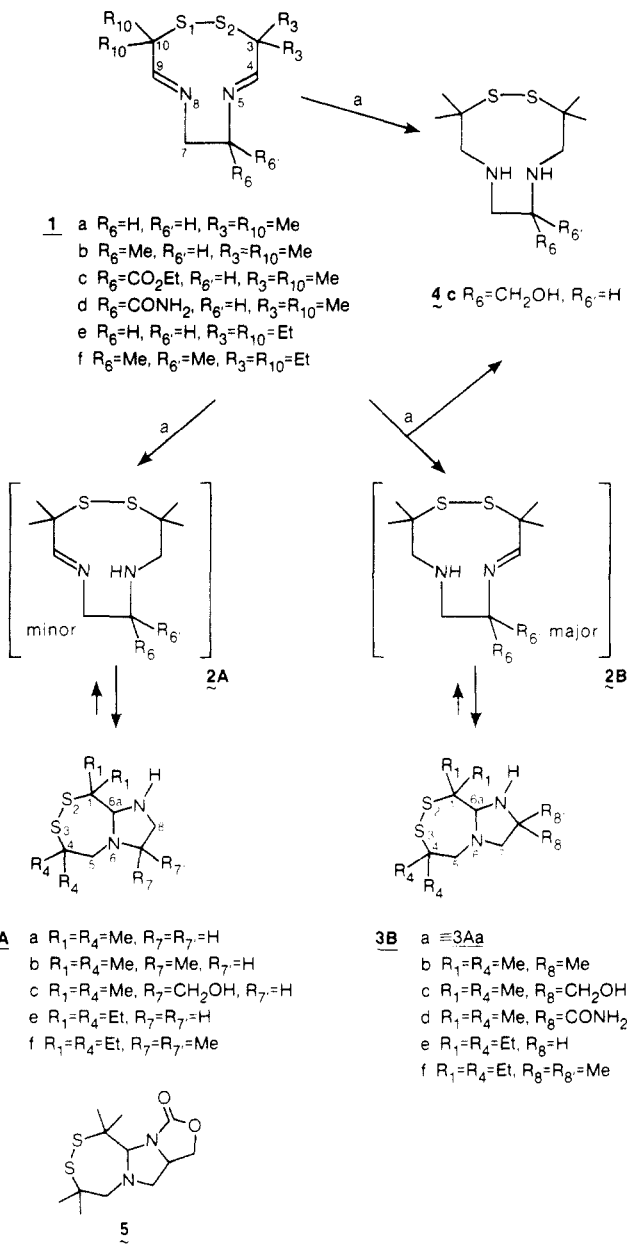
Scheme I[a]



1 a R_6=H, $R_{6'}$=H, R_3=R_{10}=Me
b R_6=Me, $R_{6'}$=H, R_3=R_{10}=Me
c R_6=CO_2Et, $R_{6'}$=H, R_3=R_{10}=Me
d R_6=$CONH_2$, $R_{6'}$=H, R_3=R_{10}=Me
e R_6=H, $R_{6'}$=H, R_3=R_{10}=Et
f R_6=Me, $R_{6'}$=Me, R_3=R_{10}=Et

4 c R_6=CH_2OH, $R_{6'}$=H

2A 2B

3A a R_1=R_4=Me, R_7=$R_{7'}$=H
b R_1=R_4=Me, R_7=Me, $R_{7'}$=H
c R_1=R_4=Me, R_7=CH_2OH, $R_{7'}$=H
e R_1=R_4=Et, R_7=$R_{7'}$=H
f R_1=R_4=Et, R_7=$R_{7'}$=Me

3B a ≡3Aa
b R_1=R_4=Me, R_8=Me
c R_1=R_4=Me, R_8=CH_2OH
d R_1=R_4=Me, R_8=$CONH_2$
e R_1=R_4=Et, R_8=H
f R_1=R_4=Et, R_8=$R_{8'}$=Me

5

[a] Reaction conditions: (a) 5 molar equiv of $NaBH_4$ in ethanol at 25 °C for 24 h.

Under the above reaction conditions the isolated yields of the bicyclic products are in the range 57% to 70% while those of the monocyclic products range from 22% to 38%. This product distribution is not substantially altered by carrying out the reduction at 50 °C for 24 h. For example 3,3,10,10-tetraethyl-1,2-dithia-5,8-diazacyclodeca-4,8-diene (**1e**)[1] upon reduction with 5 equiv of $NaBH_4$ in ethanol at 50 °C for 24 h gave 65% of the bicyclic imidazolidine and 28% of the 10-membered ring product. However, the yields of the imidazolidines were increased significantly by carrying out the reduction at 0 °C in ethanol in the above example to 94.5% of the bicyclic imidazolidine, and only a trace of the 10-membered structures were obtained. Similarly reduction of 6,6-diethyl-3,3,10,10-tetraethyl-1,2-dithia-5,8-diazacyclodeca-4,8-diene (**1f**) with 2 equiv of $NaBH_4$ at 0 °C for 8 h afforded 73.5% isolated yield of a mixture the isomeric bicyclic imidazolidines **3** (A and B) and 15% of the 10-membered product, **4**, while at 25 °C of 45% of the bicyclic imidazolidines and 53% of the 10-membered ring structure were obtained.

In view of the fact that we identified different products from those previously claimed,[1-3] we investigated the possible effects of the reaction medium. All the $NaBH_4$ reductions reported were carried out in absolute ethanol, except for **1d**, which employed 95% ethanol. In the case of **1c** reductions were carried out in both absolute EtOH and 95% EtOH. Thus the water content of the ethanol does not significantly affect the course of the reaction nor the yields.

Regiochemistry of the Reductive Cyclization of 1,2-Dithia-5,8-diazacyclodeca-4,8-dienes to Imidazolidino[1,2-*d*]dithiazepines. Regioselectivity is evident in the $NaBH_4$ reductive cyclization of unsymmetrical dithiadiazacyclodecadienes. With bis(imines) bearing a substituent at the 6 position, the major bicyclic products correspond to reduction at the less hindered imine bond. For example when the substituent is carbethoxy, as in **1c** the regioisomeric form (**3Bc**) was obtained in 57% yield, while the disfavored regioisomer (**3Ac**) was isolated in 8% yield. The reduced 10-membered ring product **4c** was also obtained in ca. 16% yield. Each regioisomer consists of ca. 50:50 mixture of cis and trans stereoisomers determined by ^1H NMR and indicated by the orientation of the CH_2OH group relative to the bridgehead proton.

	% yield	
product	in 100% EtOH	in 95% EtOH
3Ac	6	8
3Bc	65	57
4c	23	16

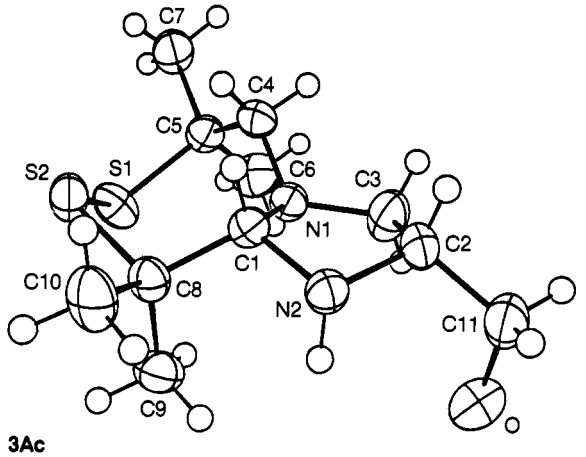
In order to distinguish **3Ac** from **3Bc** and to confirm their structures, they were treated with carbonyl diimidazole in DMF at room temperature. Isomer **3Bc** afforded the cyclic carbamate **5** (Scheme I) in 90% yield whereas isomer **3Ac** failed to react. This result is in accord with the assigned structures since the five-membered ring carbamate is expected to be formed more readily than the six-membered bridgehead carbamate. The detailed structures, stereochemistry, and conformation of the regioisomers **3Ac** and **3Bc** were determined by single-crystal X-ray analysis (see below).

In other cases additional confirmation of the bicyclic nature of the products **3** was obtained by formation of only a monoacyl derivative, e.g., the N-acetyl derivative from **3Bb**.

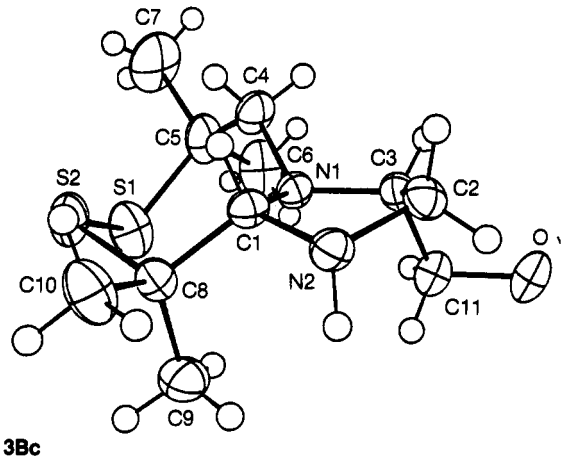
Single-Crystal X-ray Determination of Structure and Conformation of Isomeric 7- and 8-(Hydroxymethyl)-1,1,4,4-tetramethylimidazolidino[1,2-*d*]dithiazepines 3Ac and 3Bc.[15] Drawings of the two molecules are shown in Figure 1. Bond distances and angles are given in Tables I and II. The structural results clearly show the bicyclic nature of the products as well as the positions and orientations of the hydroxymethyl groups in the two isomers.

The geometries of the two molecules are entirely normal with no important differences in comparable parameters between the two compounds. The seven-membered ring contains the disulfide unit and adopts a distorted twist-

(15) The X-ray crystallographic studies were carried out by Dr. R. G. Ball at the Structure Determination Laboratory, Department of Chemistry. Enquiries regarding the crystallographic results should be directed to the above address quoting report numbers SR:121523-02-86 and 121523-04-86. (a) The diffractometer programs are those supplied by Enraf-Nonius for operating the CAD4F diffractometer with some local modifications and additions. (b) MULTAN 11/82, P. Main, L. Lessinger, M. M. Woolfson, G. Grmain, and J.-P. Declercq. Other programs used during structure refinement and analysis are part of the Enraf-Nonius Structure Determination Package by B. A. Frenz (*Computing in Crystallography*; Delft University Press: Delft, Holland, 1978; pp 64-71.



3Ac



3Bc

Figure 1. Single-crystal X-ray diffraction derived ORTEP[18] drawings of the imidazolidino[1,2-*d*]dithiazepines **3Ac** and **3Bc**. Ellipsoids of 50% probability are shown except for the hydrogens which are an arbitrary size.

chair conformation.[16a,b] Open-chain disulfides or those in large unconstrained rings typically show C–S–S–C torsion angles of 90 ± 10°[16c,d] and it is this dihedral angle that dominates the conformation of the seven-membered ring resulting in the distortion of the twist-chair configuration.

Both structures possess trans ring junctions, as expected from an anti transannular addition to the imine bond although it is conceivable that nitrogen inversion takes place. The hydroxymethyl groups are oriented trans to the bridgehead hydrogen at 6a and while in the favored 8-isomer it adopts a pseudo-equatorial position, in the 7-isomer it is aligned pseudoaxially. These forms were found in the crystals suitable for X-ray examination; however, as noted above, the ^{1}H NMR spectra of **3Ac** and **3Bc** obtained from the reaction indicated ca. 50:50 mixtures of cis- and trans-oriented products.

Reductive Cleavage of Imidazolidino[1,2-*d*]dithiazepines to 1,2-Dithia-5,8-diazacyclodecanes. Reduction of the 6-carbethoxy-1,2-dithia-5,8-diazacyclodeca-4,8-diene **1c** with 5 molar equiv of $NaBH_4$ at 40 °C for 72 h gives the isomeric 7- and 8-(hydroxymethyl)-imidazolidino[1,2-*d*]dithiazepines **3Ac** and **3Bc** in 8% and 57% yield respectively, together with 16% of the reduced 10-membered ring product **4** (R_6 = CH_2OH) (Scheme I). However, prolonged reduction under these conditions (>120 h) gives the altered product ratio of 7% **3Ac**, 33% **3Bc**, and 32% **4** (R_6 = CH_2OH). This suggested that the bicyclic structure is subject to further reduction and moreover that the regioisomeric products **3Bc** differ in their reactivity. This was confirmed by subjecting the purified isomers **3Ac** and **3Bc** to the reducing conditions of 10 molar equiv of $NaBH_4$ at 40–45 °C for 10 days. The 8-isomer **3Bc** affords a 5% yield of the 10-membered ring product, together with 95% of unreacted starting material whereas the 7-isomer **3Ac** under identical conditions gives no evidence of any further reduction.

This particular reaction was carried out on a relatively small scale. Since the reduction of the imidazolidine is very slow, presumably the $NaBH_4$ undergoes decomposition during the prolonged reaction period and in 95% EtOH at the reaction temperature of 40–45 °C, thus accounting for the low yield. Better results are obtained by adding $NaBH_4$ in portions over several days, e.g., reduction of 1,1,4,4,7,7-hexamethylimidazolidino[1,2-*d*]dithiazepine and 1,1,4,4,8,8-hexamethylimidazolidino[1,2-*d*]dithiazepine with 10 equiv of $NaBH_4$ (added in portions over 3 days) at room temperature affords 32% yield of the reduced product.

The reduction of **3Bc** presumably takes place via a low equilibrium concentration of the ring-opened 1,2-dithia-5,8-diazacyclodec-4-ene **2Bc**.[17] This indicates that the initial cyclization is reversible, at least for the 8-isomer. The fact that this equilibrium is necessary for the reduction of the imidazolidine to take place is also shown by the failure of the corresponding N,O-diacetyl derivatives to undergo reduction with ca. 20 equiv of $NaBH_4$ in ethanol at 25 °C for 72 h or at 45–50 °C for 6 days, respectively. A further example is provided by the isomeric pair **3Ab** and **3Bb** in which the 8-isomer **3Bb** undergoes reductive ring opening to **4b** (R_6 = CH_3), whereas **3Ab** is unreactive.

The relatively low yield of the tetrahydro 10-membered ring products **4** and the high recovery of unreduced imidazolidino[1,2-*d*]dithiazepines **3** following prolonged treatment with $NaBH_4$ suggests this pathway cannot account entirely for the formation of the tetrahydrodithiadiazacyclodecane product. It appears likely that concomitant monoreduction of the decadienes **1** occurs followed by cyclization of **2** to the bicyclic structures **3** as well as direct double reduction to the dithiadiazacyclodecanes. The fact that ring closure is favored at lower reaction temperatures and formation of the doubly reduced 10-membered product is favored at higher reaction temperatures is in accord with expectations of the relative activation energies of these competing processes.

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(17) Temperature variable ^{1}H NMR studies with **3Ac** and **3Bc** gave no evidence of detectable concentrations of **2Ac** or **2Bc** respectively in the temperature range −50 °C to 60 °C either in $CDCl_3$ or under basic conditions ($NaOCD_3$ in CD_3OD). The direction of opening of geminal diamines under reductive conditions has been considered by a number of authors (Ganem, B. *Acc. Chem. Res.* **1982**, *15*, 290. Moad, G.; Benkovic, S. J. *J. Am. Chem. Soc.* **1978**, *100*, 5495; **1976**, *98*, 3678. Wilson, E. M. *Tetrahedron* **1965**, *21*, 2561. Kashima, C.; Katoh, A.; Yoshiwara, N.; Omote, Y. *J. Heterocycl. Chem.* The consensus view is that the direction of reduction is dictated by formation of the less basic amine usually with concomitant generation of the more stable iminium ion. In the present example of opening of **3** to **2**, another contributing factor is that cleavage of bond 6–6a generates an uncharged species following proton loss from N_9-H, in contrast to the charged iminium species that would result from cleavage of bond 6a–9. The apparent differences in the rates of opening of **3Bc** to **2Bc** compared with the slower opening of **3Ac** to **2Ac** may reflect subtle differences in the alignment of the N_9 nonbonded lone pair with respect to the necessary antiperiplanarity to bond 6a–6 in the ring opening such as are discussed in Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: 1983, p 147 et seq.

(18) Johnson, C. K. ORTEP, ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, TN, 1965.

In conclusion, our findings have the following implications vis-a-vis the earlier literature concerning the synthesis of these compounds and their application in brain imaging.

As described in the report of Kung et al.,[1] after reduction of compounds of the type **1**, the products were acidified with HCl gas in ethanol. Fortuitously only the dithiadiazacyclodecane hydrochlorides precipitate, albeit in low yields, leaving behind the major product, the bicyclic imidazolidino[1,2-*d*]dithiazepines. In the case of **3Bc** the product was further reduced with Red-Al (Aldrich) to the dithiol by Kung et al.[3] in only 18% yield. It is conceivable that their reaction conditions also effect reduction of the imidazolidine but insufficient data are provided by the authors to substantiate their structure assignment. In the case of **3Bd** the product was treated with diborane to reduce $CONH_2$ to CH_2NH_2. In this example also reduction of the major compound, the imidazolidino[1,2-*d*]dithiazepine may have taken place fortuitiously as evidenced by the reported CIMS, 264 (M + 1, 100%).[3] It is clear however that the application of these compounds in brain imaging requires careful reassessment with regard to the actual structural components injected.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The IR spectra were recorded on a Nicolet 7199 FT spectrophotometer and only the principal, sharply defined, peaks are reported. The ^1H NMR spectra were recorded on Perkin-Elmer 90 and Varian HA-100 analytical spectrometers or on Bruker WH-200 and WH-400 spectrometers. The spectra were recorded on approximately 5–15% (w/v) solutions, depending upon the spectrometers, in appropriate deuteriated solvents with tetramethylsilane as internal standard. Line positions are recorded in ppm from reference. Wherever possible, and where overlap of signals did not interfere, the positions of the individual protons in particular regioisomers were assigned. Electron impact and chemical ionization mass spectra were determined on an Associated Electrical Industries (AEI) MS-9 and MS-50 double-focusing high resolution mass spectrometers. The peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15000. Kiesel gel DF-5 (Camag, Switzerland) and Eastman Kodak precoated sheets were used for thin layer chromatography. In the workup procedures reported for the various syntheses described, solvents were removed with a rotary evaporator under reduced pressure without heating. Kieselgel (Fluka, Switzerland) was used for column chromatography.

2,2′-Dithiobis(2-methylpropanal). This compound was prepared according to a reported method:[1] yield 55%; bp 95–97 °C (0.5 mm) (lit.[1] bp 92–93 °C (0.3 mm)).

2,2′-Dithiobis(2-ethylbutanal). This compound was prepared by a similar procedure: yield 70%; mp 71 °C (lit.[1] mp 58–59 °C).

General Procedure for the Preparation of 1,2-Dithia-5,8-diazacyclodeca-4,8-dienes. A solution of the appropriate dialdehyde (10 mmol) and appropriate ethylenediamine (10 mol) in ethanol (100%, 10 mL) was refluxed for 30 min. The mixture was concentrated in vacuo, and the residue was recrystallized from hexane. The yields and physical characteristics of the bis(imines) prepared are summarized as follows.

1a was prepared in 50% yield according to the literature procedure:[1] mp 162–163 °C (hexane) (lit.[1] mp 162–164 °C). **1b** was prepared in 53% yield by the above procedure: mp 118 °C; ^1H NMR ($CDCl_3$) δ 1.34 (d, 9 H, 3 × CH_3), 1.44 (s, 6 H, 2 × CH_3), 2.90 (t, 1 H), 2.30 (m, 1 H), 3.02 (dq, 1 H), 6.86 (d, 1 H), 6.92 (s, 1 H); IR ν_{max} ($CHCl_3$) 1650 cm^{-1} (CH=N); CIMS (*m/z*, relative intensity) 247 (11.1, M^+ + 3), 246 (15.7, M^+ + 2), 245 (100.0, M^+ + 1); EIMS (*m/z*, relative intensity) 180.1627 (78.92, $M^+ - S_2$), 138.1153 (100.0 *m/z* 180 – C_3H_6).

1c was prepared in 57% yield according to the literature procedure,[3] mp 100–101 °C.

1d was prepared in 54% yield according to the literature procedure,[3] mp 188–190 °C.

6,6-Dimethyl-3,3,10,10-tetraethyl-1,2-dithia-5,8-diazacyclodeca-4,8-diene (1f) was prepared in 69% yield: mp 106 °C; ^1H NMR ($CDCl_3$) δ 0.85 (m, 12 H, 4 × CH_3), 1.25 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.40–2.0 (m, 8 H, 4 × CH_2), 2.95 (d, 1 H), 3.85 (dd, 1 H), 6.80 (s, 1 H), 6.90 (d, 1 H); IR ($CHCl_3$) ν_{max} 1650 cm^{-1} (CH=N); MS (*m/z*, relative intensity), 316.1849 (0.08, M^+ + 2), 315.1891 (0.25, M^+ + 1), 314.1844 (0.64, M^+), calcd for $C_{16}H_{30}N_2S_2$, 314.1851, 250.2409 (11.79, $M^+ - S_2$), 212.1350 (21.05, $M^+ - C_5H_{10}S$), 180.1627 (20.61, *m/z* 212.1350 – S), 154.1597 (100.0, *m/z* 180.1627 – CN).

General Procedure for the Reduction of 1,2-Dithia-5,8-diazacyclodeca-4,8-dienes with Sodium Borohydride at 25 °C. A solution of the appropriate bis(imine) (1 mmol) in ethanol (100%, 10 mL) was stirred with sodium borohydride (20 mg, 5.26 mmol) at 25 °C for 20 h. The reaction mixture was concentrated in vacuo and the residue was partitioned between water (20 mL) and dichloromethane (20 mL). The organic layer was removed, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined extracts were washed with water (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with chloroform–methanol (19:1) gave the imidazolidines and then elution with chloroform–methanol–ammonium hydroxide (79:20:1) gave the dithiadiazacyclodecanes. In those cases where more than one imidazolidine is formed, they were separated by preparative thin layer chromatography on silica gel (chloroform–5% methanol). The dithiadiazacyclodecanes isolated were converted to the hydrochloride (HCl gas–ethanol) and recrystallized from ethanol or methanol. The yields and properties of the imidazolidines and dithiadiazacyclodecanes are summarized as follows.

Imidazolidino[1,2-*d*]dithiazepines 3. 3Aa was isolated in 69.3% yield: mp 65 °C; ^1H NMR ($CDCl_3$) δ 1.30 (q, 12 H, 4 × CH_3), 1.98 (br s, 1 H exchangeable NH), 2.6–3.10 (m, 4 H), 3.25 (m, 2 H), 3.55 (s, 1 H); IR ($CHCl_3$) 3290 cm^{-1} (NH), MS (*m/z*, relative intensity) 233.1111 (0.24, M^+ + 1), 232.1070 (1.88, M^+), calcd for $C_{10}H_{20}N_2S_2$, 232.1068, 158.0897 (93.32, $M^+ - C_3H_6S$), 125.1081 (60.23, *m/z* 158.0879 – SH), 84.0690 (100.0, $C_9H_8N_2$), 74.0193 (1.86, CH_3CSCH_3).

3Ab and 3Bb. The major product **3Bb** was isolated in 50.5% yield as an oil and as a 1:1 mixture of stereoisomers (depending on the orientation of the 8-CH_3 group): ^1H NMR ($CDCl_3$) δ 1.1–1.40 (m, 15 H, 5 × CH_3), 1.75 (s, 1 H exchangeable NH), 2.40 (t, 0.5 H), 2.60 (d, 1 H), 2.90 (d, 0.5 H), 3.30 (m, 2.5 H), 3.65 (d, 0.5 H); IR ($CHCl_3$) ν_{max} 3300 cm^{-1} (NH); MS (*m/z*, relative intensity) 247.1270 (0.20, M^+ + 1), 246.1225 (0.88, M^+), calcd for $C_{11}H_{22}N_2S_2$ 246.1224, 172.1036 (100.0, $M^+ - C_3H_6S$), 157.0805 (71.96, *m/z* 172.1036 – CH_3), 139.1237 (34.08, *m/z* 172.1036 – SH), 98.0865 [62.02, $M^+ - 2 \times (CH_3CSCH_3)$], 74.0194 (2.24, CH_3CSCH_3). The isomer **3Ab** was isolated in <7% yield as an oil: IR ($CHCl_3$) ν_{max} 3300 cm^{-1} (NH); CIMS (*m/z*, relative intensity) 249 (7.9, M^+ + 3), 248 (15.3, M^+ + 2), 247 (100, M^+ + 1).

3Ac and 3Bc. Compound **3Ac** was isolated from the reduction in 57% yield: mp 55 °C and 85 °C ($CHCl_3$/hexane); ^1H NMR ($CDCl_3$) δ 1.30 (m, 12 H, 4 × CH_3), 2.15 (br s, 2 H, exchangeable NH, OH), 2.50 (q, 1 H), 2.65 (t, 0.5 H), 2.95 (t, 0.5 H), 3.05 (q, 0.5 H), 3.2–3.65 (m, 5.5 H). (The nonintegral proton intensities are due to the 50:50 mixture of cis and trans stereoisomers relative to the 8 substituent); IR ($CHCl_3$) ν_{max} 3330 cm^{-1} (NH, OH); CIMS (*m/z*, relative intensity), 265 (11.4, M^+ + 3), 264 (16.9, M^+ + 2), 263 (100.0, M^+ + 1).

Further elution of the silica gel column with EtOAc/MeOH afforded regioisomer **3Ac** as a crystalline solid: mp 110–112 °C ($CHCl_3$/hexane) in 8% yield; ^1H NMR ($CDCl_3$) δ 1.1–1.60 (m, 12 H, 4 × CH_3), 2.30 (br s, 2 H, exchangeable NH, OH), 2.65–3.70 (m, 7.5 H), 4.05 (s, 0.5 H) (The nonintegral proton intensities arise from the 50:50 mixture of cis and trans stereoisomers relative to the 7 substituent); IR ($CHCl_3$) ν_{max} 3420–3300 cm^{-1} (NH, OH); CIMS (*m/z*, relative intensity) 265 (12.0, M^+ + 3), 264 (16.4, M^+ + 2), 263 (100.0, M^+ + 1).

3Bd. Compound **3Bd** was isolated as the only regioisomeric product in 85% yield: mp 140 °C; ^1H NMR ($CDCl_3$) δ 1.30 (m, 12 H, 4 × CH_3), 2.2–2.6 (br s, q 2 H, 1 H exchangeable), 2.9–3.4 (m, 2 H), 3.5–3.95 (m, 3 H), 5.60 (br s, 1 H exchangeable), 7.05 (br s, 1 H exchangeable); IR (Nujol) ν_{max} 3400–3320 (NH, NH_2), 1670 cm^{-1} ($CONH_2$); CIMS (*m/z*, relative intensity), 278 (13.0, M^+ + 3), 277 (16.6, M^+ + 2), 276 (100.0, M^+ + 1).

8,8-Dimethyl-1,1,4,4-tetraethylimidazolidino[1,2-*d*]-dithiazepine (3Bf) was isolated as an oil (yield 16%): ^1H NMR

($CDCl_3$) δ 0.85 (m, 12 H, 4 × CH_3), 1.0 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.3–1.80 (m, 8 H, 4 × CH_2), 2.05 (br s, 1 H, NH exchangeable), 2.55 (s, d, 3 H), 2.80 (d, 1 H), 3.88 (s, 1 H); IR ($CHCl_3$) ν_{max} 3350 cm^{-1} (NH); MS (m/z, relative intensity) 318.1983 (0.23, $M^+ + 2$), 317.2028 (0.46, $M^+ + 1$), 316.2088 (2.05, M^+), calcd for $C_{16}H_{32}N_2S_2$, 316.2007, 214.1504 (46.06, $M^+ - C_2H_5CSC_2H_5$), 181.1706 (100.0, 214.1504 - SH), 112.1027 [80.32, M^+ - 2-($C_2H_5CSC_2H_5$), 102.0507 (1.93, $C_2H_5CSC_2H_5$).

7,7-Dimethyl-1,1,4,4-tetraethylimidazolidino[1,2-*d*]dithiazepine (3Af) was isolated as an oil (yield, 29%): ^1H NMR ($CDCl_3$) δ 0.80–1.06 (m, 12 H, 4 × CH_3), 1.10 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.38–1.85 (m, 9 H, 4 × CH_2 + NH, 1 H exchangeable), 2.60 (d, 1 H), 2.80 (d, 1 H), 2.95 (d, 1 H), 3.20 (d, 1 H), 4.05 (s, 1 H); IR ($CHCl_3$) ν_{max} 3350 cm^{-1} (NH); CIMS (m/z, relative intensity), 319 (12.2, $M^+ + 3$), 318 (21.4, $M^+ + 2$), 317 (100, $M^+ + 1$).

1,1,4,4-Tetraethylimidazolidino[1,2-*d*]dithiazepine (3Ae) was isolated in 59.5% yield as an oil: ^1H NMR ($CDCl_3$) δ 1.0 (m, 12 H, 4 × CH_3), 1.30–1.95 (m, 8 H, 4 × CH_2), 2.0 (br s, 1 H, exchangeable NH), 2.30 (m, 1 H), 2.86 (m, 2 H), 3.00 (m, 2 H), 3.20 (m, 2 H), 4.03 (s, 1 H); IR ($CHCl_3$) 3320 cm^{-1} (NH); MS (m/z, relative intensity) 288.1719 (0.24, M^+), calcd for $C_{14}H_{28}N_2S_2$, 288.1694, 224.2247 (1.59, $M^+ - S_2$), 186.1192 (54.39, $M^+ - C_5H_{10}S$) 157.0802 (22.10, m/z 186.1192 - C_2H_5), 153.1393 (100.0, $C_9H_{17}N_2$).

1,2-Dithia-5,8-diazacyclodecanes 4. 4A was isolated in 22.2% yield from the $NaBH_4$ reduction of **1** as the dihydrochloride salt: mp 230–250 °C dec (lit. mp 255–256 °C).

4b was isolated in 38% yield from the reduction of **1** as the dihydrochloride salt: mp 220–235 °C dec; ^1H NMR (D_2O) δ 1.40 (m, 15 H, 5 × CH_3), 3.10 (dd, 1 H), 3.2–3.95 (m, 6 H); IR ($CHCl_3$) ν_{max} 3290, 3330 cm^{-1} (NH); MS (m/z, relative intensity) (free base) 250.1346 (3.31, $M^+ + 2$), 249.1408 (5.14, $M^+ + 1$), 248.1381 (35.58, M^+), calcd for $C_{11}H_{24}N_2S_2$, 248.1381, 131.0768 (22.96, $C_6H_{13}NS$), 116.0535 (45.72, $C_5H_{10}NS$), 99.0966 (20.23, $C_5H_{11}N_2$), 57.0601 (100.0, C_3H_7N).

4c (R_6 = CH_2OH) was isolated in 16% yield from the $NaBH_4$ reduction of **1c** as a crystalline solid: mp 105 °C ($CHCl_3$/hexane); ^1H NMR ($CDCl_3$) δ 1.30 (m, 12 H, 4 × CH_3), 2.2–3.65 (m, 12 H, 3 protons exchangeable); IR ($CHCl_3$) ν_{max} 3340–3260 cm^{-1} (NH, OH); CIMS (m/z, relative intensity) 267 (11.8, $M^+ + 3$), 266 (16.7, $M^+ + 2$), 265 (100.0, $M^+ + 1$).

4d was isolated in ~1% yield from the $NaBH_4$ reduction of **1d** as a crystalline solid: mp 180 °C; ^1H NMR ($CDCl_3$) δ 1.25 (m, 12 H, 4 × CH_3), 1.90 (br s, 2 H, exchangeable NH), 2.45 (d, 1 H), 2.65–3.20 (m, 6 H), 5.30 (br s, 2 H, exchangeable NH_2); CIMS (m/z, relative intensity) 280 (11.3, $M^+ + 3$), 279 (16.1, $M^+ + 2$), 278 (100.0, $M^+ + 1$).

6,6-Dimethyl-3,3,10,10-tetraethyl-1,2-dithia-5,8-diazacyclodecane dihydrochloride: mp 225 °C (yield, 53%); ^1H NMR (D_2O) δ 0.95 (m, 12 H, 4 × CH_3), 1.42 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 1.55–1.90 (m, 8 H, 4 × CH_2), 3.2–3.45 (dd, s, 4 H), 3.60 (d, 2 H); IR ($CHCl_3$) ν_{max} (free base) 3320, 3280 cm^{-1} (NH); MS (free base) (m/z, relative intensity), 320.2134 (0.72, $M^+ + 2$), 319.2195 (1.42, $M^+ + 1$), 318.2163 (6.78, M^+), calcd for $C_{16}H_{34}N_2S_2$, 318.2163, 173.1238 (69.75, $C_9H_{19}NS$), 158.1004 (39.08, m/z 173.1238 - CH_3), 140.1438 (100.0, m/z 173.1238 - SH), 71.0736 (27.51, C_4H_9N).

General Procedure for the Acetylation of Bicyclic Imidazolidines and Dithiadiazacyclodecanes. A mixture of the appropriate amino compound (1 mmol), acetic anhydride (5 mmol), and dry pyridine (5 mL) was stirred at 25 °C for 20 h. The solvents were removed in vacuo and the residue was recrystallized from hexane. The yields, mp, and physical data are summarized as follows.

3Be: 92% yield; mp 103 °C (hexane); ^1H NMR ($CDCl_3$) δ 1.30 (t, 12 H, 4CH_3), 2.10 (s, 3 H, $COCH_3$), 2.20 (s, 3 H, $COCH_3$), 2.50 (d, 1 H), 3.0 (q, 1 H), 3.15 (d, 1 H), 3.45 (d, 1 H), 4.10 (q, 1 H), 4.20–4.40 (m, 2 H), 4.70 (s, 1 H); IR ($CHCl_3$) ν_{max} 1750 ($OCOCH_3$), 1670 cm^{-1} ($NCOCH_3$); MS (m/z, relative intensity) 347.1413 (0.09, $M^+ + 1$), 346.1383 (0.25, M^+), calcd for $C_{15}H_{26}N_2O_3S_2$, 346.1385, 272.1198 (42.9, $M^+ - C_3H_6S$), 199.0897 (100, m/z 272.1198 - CH_2OCOCH_3).

3Bf: 97% yield; mp 122–125 °C (hexane); ^1H NMR ($CDCl_3$) δ 1.25 (dd, 15 H, 5 × CH_3), 2.1 (s, 3 H, $COCH_3$), 2.45 (d, 1 H), 3.0 (q, 2 H), 3.45 (d, 1 H), 4.0 (m, 1 H), 4.70 (s, 1 H); IR ($CHCl_3$) 1660 cm^{-1} (NCO); MS (m/z, relative intensity) 290.1311 (0.18, $M^+ + 2$), 289.1375 (0.47, $M^+ + 1$), 288.1336 (2.4, M^+), calcd for $C_{13}H_{24}N_2S_2O$, 288.1330, 214.1142 (100.0, $M^+ - CH_3CSCH_3$), 199.0908 (61.56, m/z 214.1142 - CH_3), 181.1343 (21.65, m/z 214.1142 - SH), 140.0952 (42.21, $M^+ - 2 \times CH_3CSCH_3$), 74.0195 (2.51, CH_3CSCH_3).

Preparation of Cyclic Carbamate 5. A solution of **3Bc** (134 mg, 0.5 mmol) in 10 mL of dry DMF was treated with 1,1'-carbonyldiimidazole (81 mg, 0.5 mmol). The mixture was stirred at room temperature for 12 h and then the solvent was removed in vacuo at 80 °C. The solid residue was subjected to column chromatography over silica gel and eluted with $CHCl_3$. The white solid obtained was recrystallized from $CHCl_3$/hexane: 120 mg (yield 90%) mp 183 °C; ^1H NMR ($CDCl_3$) δ 1.2–1.65 (m, 12 H, 4 × CH_3), 2.6 (d, 1 H), 2.75 (q, 1 H), 3.35 (q, 2 H), 4.05 (m, 1 H), 4.15 (s, 1 H), 4.25 (q, 1 H), 4.5 (q, 1 H); IR ($CHCl_3$) ν_{max} 1751 cm^{-1} (-NCO); MS (m/z, relative intensity) 290.0937 (1.38, $M^+ + 2$), 289.0998 (2.66, $M^+ + 1$), 288.0967 (10.4, M^+) calcd for $C_{12}H_{20}N_2S_2O_2$, 288.0966, 214.0772 (100, $M^+ - C_3H_6S$), 140.0589 (60.07, $C_6H_8N_2O_2$).

X-ray Crystallography.[15] Single crystals of the 7-isomer **3Ac** were prepared by the diffusion method of slow introduction of hexane vapor into a $CHCl_3$ solution. Single crystals of the 8-isomer **3Bc** were prepared by chilling an ether solution.

Crystal data for 8-isomer 3Bc: $C_{11}H_{22}N_2OS_2$; M_r 262.44; monoclinic, $P2_1/c$, a = 9.722 (3), b = 5.859 (3), and c = 24.583 (4) Å, β = 97.33 (2)°, V = 1389 Å^3, Z = 4; monochromatized Mo Kα radiation (λ = 0.71073 Å); data were collected on a CAD4F diffractometer[15a] using an ω–2θ scan to a 2θ limit of 54° at 23 °C; 3343 unique data with 1685 observed at $I > 3\sigma(I)$; structure was solved by using direct methods;[15b] final unweighted and weighted R values were 0.050 and 0.063, respectively; highest peak in a final difference Fourier was 0.38 (7) e Å^{-3} with no chemical significance.

Crystal data for 7-isomer 3Ac: $C_{11}H_{22}N_2OS_2$; M_r 262.44; monoclinic, $P2_1/c$, a = 16.317 (3), b = 7.054 (1), and c = 12.464 (3) Å, β = 107.50 (2)°, V = 1368.2 Å^3, Z = 4; monochromatized Mo Kα radiation (λ = 0.71073 Å); data were collected on a CAD4F diffractometer[15a] using an ω–2θ scan to a 2θ limit of 54° at 23 °C; 3025 unique data with 1518 observed at $I > 3\sigma(I)$; structure was solved by using direct methods;[15b] final unweighted and weighted R values were 0.042 and 0.052, respectively; Highest peak in a final difference Fourier was 0.49 (6) e Å^{-3} with no chemical significance.

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Supplementary Material Available: X-ray crystallographic data (18 pages). Ordering information is given on any current masthead page.