6,16-Methano-6*H*,16*H*-[2,4]benzothiazepino[3,4-*d*][1,3,5]benzoxadiazocine and 6,26:13,19-Dimethano-6*H*,9*H*,13*H*,19*H*,22*H*,26*H*-benzo[1",2":5,6;4",5":5',6']bis[1,3]thiazepino[2,3-*d*:2',3'-*d*']bis[1,3,5]-benzoxadiazocine: New Heterocyclic Systems

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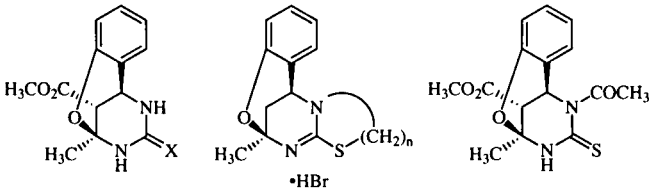
Received December 2, 1998

Cyclization reactions of oxygen-bridged pyrimidinethione **1a** with 1,2-bis(bromomethyl)benzene and 1,2,4,5-tetrakis(bromomethyl)benzene leading to conformationally restricted benzothiazepine derivatives were examined. Molecular conformations of the products were studied by 1D and 2D nmr spectroscopy and with the help of semiempirical calculations.

J. Heterocyclic Chem., **36**, 1023 (1999).

As a part of our ongoing project on conformationally restricted heterocycles we have recently described a highly diastereoselective cyclocondensation of a Biginelli type leading exclusively to oxygen-bridged pyrimidines **1a** and **1b** [1,2] (Scheme 1). The thioxo ester **1a** possessing a thioureido moiety was found to be a useful building block for the construction of polycyclic systems. Its cyclization with α,ω-dibromoalkanes permitted a synthetic entry into fused heterocycles **2** with 5-, 6- or 7-membered ring annelated to the fundamental skeleton [1]. All these compounds were evaluated in the preliminary screening within the NCI *In Vitro* Anti-AIDS Drug Discovery Program at the National Cancer Institute, Bethesda. However, none of them displayed substantial antiviral activity. On the other hand, 5-acetyl-3,4,5,6-tetrahydro-2,6-methano-4-thioxo-2*H*-1,3,5-benzoxadiazocine-11-carboxylate derivative **3** revealed remarkable behaviour as a probe of the dihydropyridine receptor in a radioligand binding study with [^{3}H]nitrendipine [3].



1a: X = S
1b: X = O

2: n = 2,3,4

3

Recently it was demonstrated that the cardiovascular drug diltiazem, a calcium antagonist, and structurally related 1,5-benzothiazepines could be useful to potentiate the antitumor activity of neoplastic agents daunorubicin, doxorubicin and vincristine [4]. Some of these stimulators are even effective alone in treating cancer metastasis [5] or AIDS [6]. Moreover, a number of calcium channel blockers have been described to exhibit antioxidant effects against free radical injury in endothelial cells [7]. These intriguing pharmacological properties inspired us to further explore the heterocyclic framework **1** for designing novel congeneric structures of potential biological importance. In the present article we report a convenient preparative route to rigid polycyclic oxygen-bridged pyrimidines incorporating the benzothiazepine nucleus.

To build up the target seven-membered ring onto the parent heterocycle we have used the same strategy as described previously [1]. Elaboration of such an additional ring was based upon cyclization of compound **1a** with reactive 1,4-dihalides. For this purpose we employed appropriate bromo derivatives of the benzylic type. In practice, the reactions were carried out according to the previously reported protocol [1]. Thus, treating pyrimidinethione **1a** and 1,2-bis-(bromomethyl)benzene in refluxing *N,N*-dimethylformamide for 45 minutes gave rise to the desired product **4** isolated as hydrobromide (Scheme 2). We have found that the heterocyclization was accompanied with loss of the methoxycarbonyl group. Apparently, the vigorous conditions, the solvent employed, and the presence of liberated hydrogen bromide are responsible for a Krapcho decarboalkoxylation [8]. An analogous behaviour of the ester **1a** in cycloalkylations has been shown by us already [1].

The ^{1}H and ^{13}C nmr spectra of compound **4** were in good agreement with the proposed structure. The significant spectral parameters are collected in Table 1. The assignment was inferred from the results of 1D and 2D methods and supported by comparison with the data obtained for the parent heterocycle **1** and its derivatives **2**. Thus, the presence of an ABX splitting pattern from the CH_2CH moiety and two AB spin systems of isolated CH_2 groups could be easily recognized in the ^{1}H nmr spectrum. Signals belonging to individual *ortho*-disubstituted benzene rings were distinguished using H,H-COSY. However, only the phenyleneoxy unit occurred as a typical ABCD framework

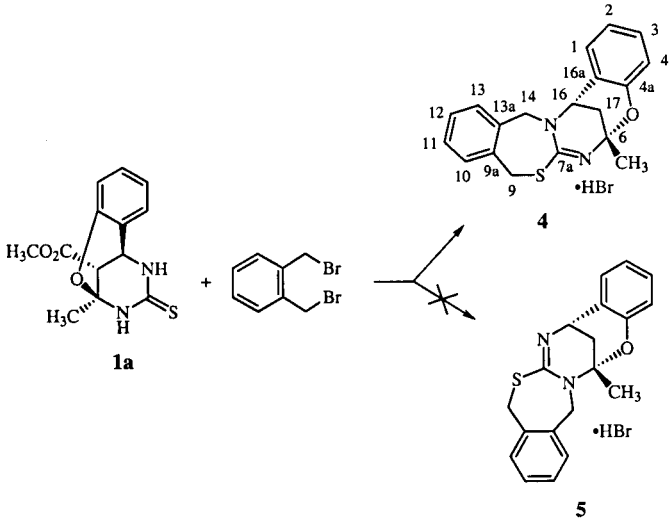
Table 1

NMR Spetral Parameters of Compound **4** (dimethyl-d_6 sulfoxide)

Atom	δ_C (ppm)	δ_H (ppm)	J_{HH} (Hz)	H,C-corr. [a]
1	129.7	7.78	7.5 (1, 2) 1.7 (1, 3)	3, 4a, 16, 16a
2	121.4	7.02	7.5 (2, 3) 0.9 (2, 4)	1, 3, 4, 4a, 16a
3	130.9	7.31	8.2 (3, 4)	1, 2, 4, 4a, 16a
4	116.7	6.90		2, 4a, 16, 16a
4a	150.5			
6	80.3			
7a	163.4			
9	33.0	4.65 (9A) 4.76 (9B)	14.5 (9A, 9B)	7a, 9a, 10, 13a
9a	135.2			
10	127.9	7.38-7.39 [b]		
11	129.6	7.38-7.39 [b]		
12	128.7	7.38-7.39 [b]		
13	129.6	7.76 [b]		11, 12, 13a, 14
13a	136.3			
14	54.0	5.37 (14A) 5.41 (14B)	15.2 (14A, 14B)	7a, 9a, 13, 13a, 16
16	56.7	5.47	3.1 (16, 17A) 2.9 (16, 17B)	1, 4a, 6, 7a, 14, 17
16a	119.4			
17	29.8	2.32 (17A) 2.36 (17B)	13.9 (17A, 17B)	16, 16a
CH_3	24.3	1.73		4a, 6, 7a, 17
NH		10.76		7a, 17

[a] Long-range H,C correlations (^{1}H–first column, ^{13}C–last column). [b] Signals were not resolved

whose analysis was based on signal multiplicities, known substituent additivity parameters, and H-H connectivity defined by the above COSY experiment. In contrast, the other *ortho*-phenylene fragment exhibited two unresolved resonances with an integral intensity 3:1, the smaller one being overlapped with a doublet of the H-1 proton. Since from the NOESY and HMBC spectra the eclipsed aromatic proton was found to be H-13, the remaining H-10, H-11 and H-12 protons were assigned to the more intensive resonance. The H,C-COSY (HETCOR) technique allowed us to determine unequivocally all protonated carbons except for those which were related to the above unresolved three aromatic protons. The latter had to be assigned by HMBC. The occurrence of a diagnostic peak at δ_C 80.3, indicating a hemiaminal C(O)N carbon [1], confirmed that the bridged substructure was retained. Also the chemical shift values observed for the quaternary isothioureido carbon (C-7a) and both C_{ipso} atoms (C-4a and C-16a) originating from the phenyleneoxy part were consistent with our earlier study [1]. Owing to the similar substituent effects of thiomethylene and aminomethylene groups, the chemical shifts of the adjacent benzene carbons C-9a and C-13a are very close and could be differentiated by HMBC experiment. Furthermore, three bond H,C-correlations between H-14 and C-16 as well as H-16 and C-14 confirmed the outlined cyclization pathway and eliminated an alternative annelation mode to the hemiaminal nitrogen atom, which would lead to compound **5** (Scheme 2).



An inspection of Dreiding models showed that molecule **4** had a relatively rigid stereochemistry. The *O*-benzene ring is held by an oxygen-bridge in a pseudoaxial and orthogonal orientation relative to the pyrimidine nucleus, while both the nitrogen and oxygen six-membered heterocycles assume fixed unsymmetrical half-chair conformations [2]. The partially saturated 1,3-thiazepine, flanked by two compact blocks, can adopt a locked chair-like form which is slightly flattened at the trigonal isothioureido flap. Nevertheless, considering the configuration at the fixed bridgehead sp^3 nitrogen atom, two such conformational structures are possible in which the pseudoaxial aminomethylene and thiomethylene hydrogens are parallel and point out above **4A** or below **4B** the average plane of the seven-membered skeleton, while the nitrogen lone electron pair is on the opposite side (Figure 1). The thiazepine ring could also be envisaged as twisted chairs **4C** and **4D** having the *anti* oriented pseudoaxial methylene hydrogens.

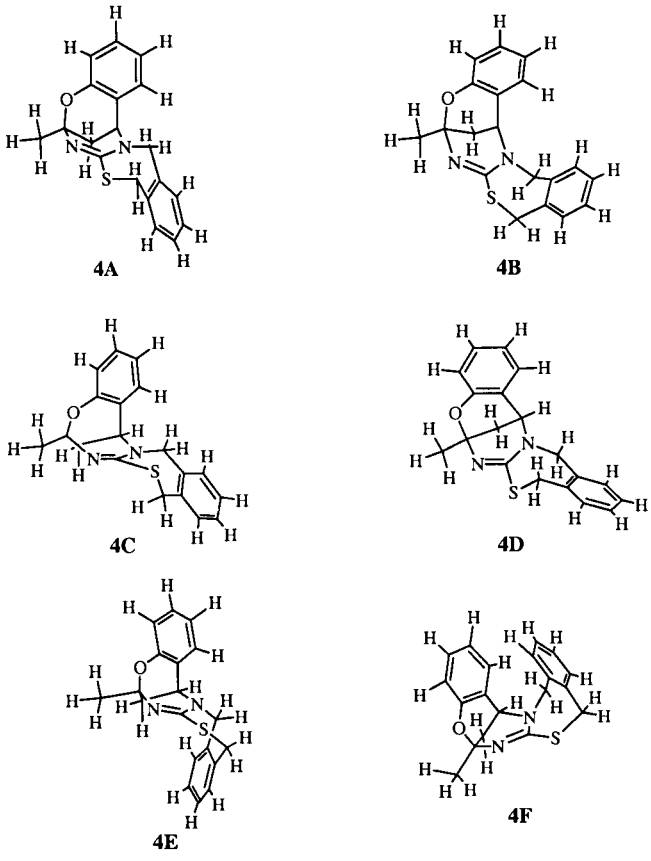


Figure 1. Possible Conformations of Compound **4**.

Finally, one of the two thiazepine boat conformations places the *ortho*-xylylene group under the pyrimidine nucleus imparting thus a sandwich-like shape to the molecule **4E**. Apparently, in this case an upfield shift of the methyl resonance, compared to that in fused heterocycles **2**, should be expected due to a ring current shielding. In turn, the inversely oriented boat form **4F** forces the outside benzenes to be stacked in an edge-to-face fashion whereby the H-1 and H-13 atoms are almost in touch. Therefore both these congested boat conformers (and twisted structures derived from them) seem to be unfavourable.

Because the solution nmr spectra at room temperature resolved the individual pseudoaxial and pseudoequatorial protons in the seven-membered ring and showed no line-broadening, it was assumed that the heterocycle **4** did not exist as rapidly equilibrating conformations. From the analysis of molecular models it followed that each of the invoked conformers **4A**, **4B**, **4C**, and **4D** would have a distinct spatial H–H relationship to be distinguished by the NOE experiment. Besides the short interproton distances pertinent to both chair structures **4A** and **4B** (H-9_{ax}–H-14_{ax}, H-1–H-16, H-14_{eq}–H-16, and H-13–H-14_{eq}), the former was expected to exhibit a closer contact between H-1 and H-14_{eq} whereas the latter would have a contact between H-14_{ax} and H-17_{ax}. On the other hand, in the case of **4C** and **4D** the essential pseudoaxial protons H-9_{ax} and H-14_{ax} are too remote to afford any NOE. Because the lines of some relevant protons almost completely overlapped when the spectra were measured in hexadeuteriodimethyl sulfoxide, we sought another solvent for the NOE measurements. Tetradeuteromethanol gave a better signal separation so that even aromatic protons H-1 and H-13 were resolved. A NOESY map showed a crucial cross-peak due to H-1–H-14_{eq} interaction while no correlation between H-14_{ax} and H-17_{ax} was found. In addition to ^{1}H–^{1}H dipole-dipole interactions observed for the pairs H-9_{ax}–H-14_{ax}, H-1–H-16, H-14_{eq}–H-16 and H-13–H-14_{eq}, a relation between the methyl and the NH protons was also determined. This indicated that the N-7 atom was protonated. Interestingly, a significant correlation was found for the relatively remote protons H-13 and H-16. The last, quite unexpected, cross-peak detected in the NOESY spectrum corresponded to a H-1–H-13 interaction (also confirmed by 1D NOE difference). This surprising correlation pointed out that the inside aromatic protons are spatially close and hence another type of molecular conformation must be considered. Although all observed NOEs would fit the boat structure **4F**, its existence, as noted above, has been ruled out. However, considering a possibility of p,π-conjugation of a p orbital on the ring junction nitrogen with the adjacent C=N double bond, a modified model having a sp^2-like bridgehead nitrogen atom could be postulated for **4G** as a more probable one. Such an electronic effect, reinforced by the N-7 atom protonation, should relieve steric crowding in the molecule. A computer-generated drawing of the AM1 optimized geometry [9] of **4G** is shown in Figure 2. To verify the proposed stereochemical model, an X-ray diffraction analysis was performed [10]. The crystal data confirmed entirely the proposed conformation **4G** and also proved that the N-15

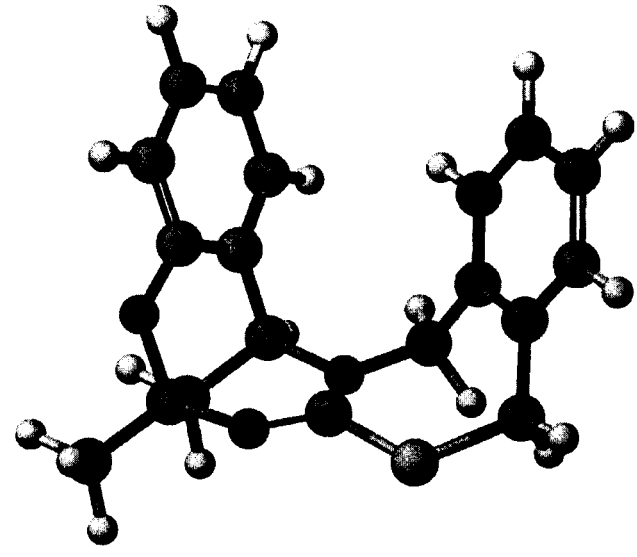
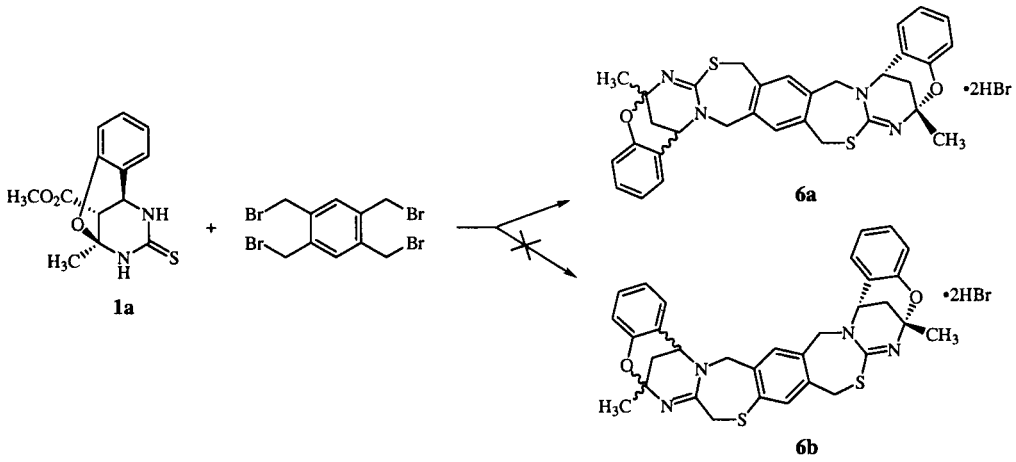


Figure 2. Minimum Energy Conformation for Structure **4G**.

atom was trigonal planar. Nevertheless, the relatively weak NOE interaction between H-1 and H-13 does not correspond fully to the interproton length determined from the solid-state structure (~ 2.3 Å). This suggested that the outside aromatic rings of structure **4G** could be more remote in a solution.

We have also attempted to incorporate the parent compound **1** in an extended, doubly oxygen-bridged system. Two pyrimidinethione units could be linked by a benzene spacer employing the described condensation method. Thus, treating the commercially available 1,2,4,5-tetrakis-(bromomethyl)benzene with **1a** yielded the expected fused analogue **6**. In contrast to the benzothiazepine **4** which had to be isolated after work-up, product **6** precipitated during the reaction. Its elemental analysis agreed with the empirical formula of $C_{32}H_{32}Br_2N_4O_2S_2$ corresponding to a 2:1 adduct formed as a salt with two molecules of hydrogen bromide. Similarly to the former heteroannelation reaction, a decarboalkoxylation took place in **6**. Nevertheless, traces of monoester derivative of **6** were detected by mass spectrometry but could not be observed in the nmr spectrum of the crude product. Taking into account the relative stereochemistry of the starting compound **1a**, there are two pairs of isomeric structures for **6** arranged either in a head-to-tail (**6a**) or a head-to-head (**6b**) fashion (Scheme 3).



The ^1H nmr spectrum of substance **6** was relatively simple. Both oxygen-bridged pyrimidines as well as both thiazepine portions exhibited only one set of resonances. The corresponding chemical shifts and coupling patterns were very similar to those observed for heterocycle **4** (Table 2). Further, two aromatic protons from the central benzene ring occurred as a singlet. The remarkable simplicity of this

Table 2

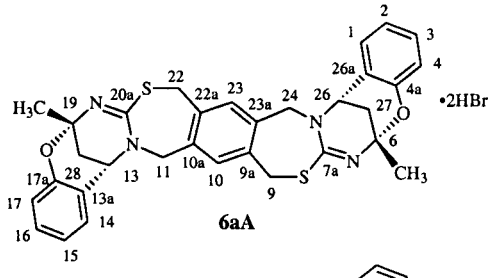
NMR Spectral Parameters [a] of Compound **6aB** (dimethyl-d_6 sulfoxide)

Atom	δ_C (ppm)	δ_H (ppm)	J_{HH} (Hz)
1, 14	129.3	7.69	7.6 (1, 2) 1.7 (1, 3)
2, 15	121.4	6.99	7.5 (2, 3) 1.2 (2, 4)
3, 16	131.0	7.28	8.0 (3, 4)
4, 17	116.8	6.88	
4a, 17a	150.4		
6, 19	80.3		
7a, 20a	163.5		
9, 22	32.7	4.73 (9A) 4.75 (9B)	14.4 (9A, 9B)
9a, 22a	136.2 [b]		
10, 23	129.5	7.75	
10a, 23a	136.6 [b]		
11, 24	53.2	5.36 [c]	14.0 (11A, 11B)
13, 26	56.6	5.44	3.0 (26, 27A) 3.0 (26, 27B)
13a, 26a	119.2		
27, 28	29.7	2.32 (27A) 2.33 (27B)	14.0 (27A, 27B)
6-CH_3, 19-CH_3	24.3	1.74	
NH		10.84	

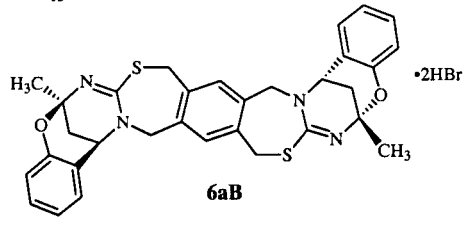
[a] Given values are identical for the symmetry-related atoms. [b] Assignments may be reversed. [c] Inner lines of an AB quartet were not resolved.

spectrum indicated symmetrical character of the molecule. Moreover, only sixteen carbon signals were found in the ^{13}C nmr spectrum for thirty two carbon atoms reflecting molecular symmetry. In order to exclude the possibility of an accidental shift degeneracy an ASIS experiment was carried out. However, no splitting of ^{1}H or ^{13}C resonances was observed after addition of hexadeuterobenzene to the sample in hexadeuteriodimethyl sulfoxide solution. On the other hand, the aromatic protons of the central benzene ring are chemically nonequivalent in the regioisomer **6b** and therefore two signals must be expected. These findings allowed us to attribute unambiguously the head-to-tail structure **6a** to the reaction product **6** while the head-to-head alternative **6b** was ruled out. Note that attempts to detect the other isomer **6b** in the reaction mixture were unsuccessful.

Heterocyclization leading to **6a** can give two possible stereoisomers with the flanking benzene rings positioned either *syn*-**6aA** or *anti*-**6aB** (Scheme 4). As seen, both structures fulfil symmetrical properties deduced from the nmr spectra. Since molecule **6aA** possesses a C_2 axis, the corresponding proton pairs are homotopic and isochronous, as well. In contrast, the latter **6aB** contains a center of symmetry, whereby corresponding nuclei pairs became internally enantiotopic and hence isochronous again.



6aA



6aB

Considering the presence of different symmetry elements, the molecule **6aA** belonging to the C_2 point group is chiral and is formed as a racemate whereas the structure **6aB** with S_2 symmetry represents an achiral entity. Unfortunately, there are no significant NOE characteristics to discern between isomers **6aA** and **6aB**. In principle, this problem would be solvable by means of chiral lanthanide shift reagents or hplc on chiral stationary phases [11]. However, low solubility of compound **6a** prevented us from employing such methods. Since we were not able to grow a suitable crystal for an X-ray analysis, a semiempirical molecular orbital treatment has been used to predict the thermodynamically favourable form.

Due to essentially identical nmr spectral data of **6a** and **4G**, it is highly probable that a molecular shape of derivative **6a** will retain the significant conformational features of **4G**. Therefore structure **4G** was chosen to build up starting conformations of **6aA** and **6aB** for their geometry optimization. The results of AM1 and PM3 calculations [9] are presented in Table 3. As can be seen, isomer **6aB** is more stable than **6aA**. The greater stability of **6aB** is tentatively assigned to its less crowded structure compared to the cage-like structure **6aA** (Figures 3 and 4).

Table 3

Heats of Formation (kcal/mol) for the Isomers **6aA** and **6aB**

Method	ΔH_f (**6aA**)	ΔH_f (**6aB**)	$\Delta\Delta H_f$
AM1	110.78	108.84	1.94
PM3	69.53	68.54	0.99

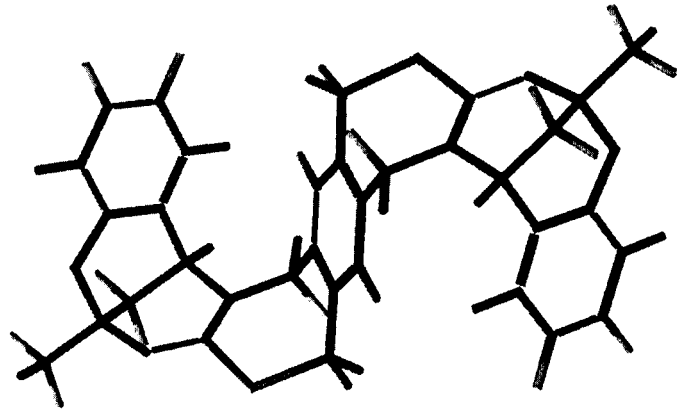


Figure 3. AM1 Optimized Geometry of Isomer **6aB**.

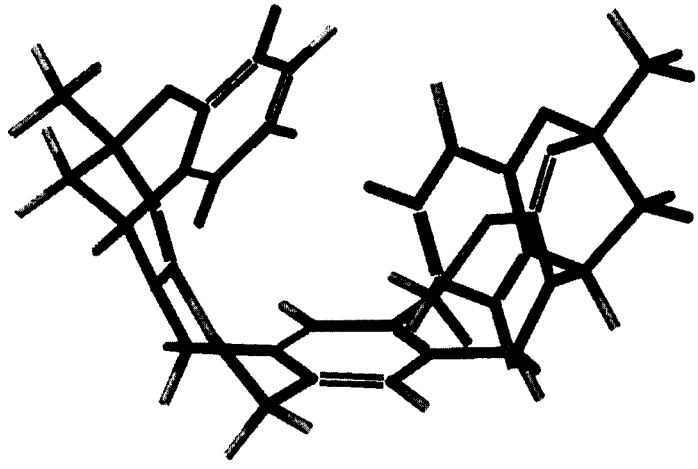


Figure 4. AM1 Optimized Geometry of Isomer **6aA**.

In conclusion, thiazepine derivatives **4** and **6aB** constitute a new class of polycondensed heterocyclic ring systems. The polycyclic molecule **6aB** proves to be another example of annelated, conformationally constrained heterocycles flanked by two oxygen-bridged pyrimidines, as reported recently from our laboratory [12].

EXPERIMENTAL

The melting points (uncorrected) were determined with a Kofler hot stage microscope. The ir spectra were recorded on a Nicolet Impact 400 D spectrophotometer. The mass spectrum (EI) of **4** was obtained on a Jeol JMS D-100 spectrometer operating at 75 eV. The hydrobromide salt was pulverized with substoichiometric amount of potassium carbonate and then evaporated from opened capillary in direct inlet. Peak matching with perfluorokerosene as the reference was utilized for hrms. The mass spectrum (FAB) of **6aB** was registered on a Finnigan MAT 95 spectrometer (Xe, 6 keV, 2 mA). 3-Nitrobenzyl alcohol was used as a sample matrix. Most of the nmr spectra of compound **4** were obtained on a Varian VXR-300 spectrometer equipped with a multinuclear broadband probe and operating at 299.943 MHz for ^{1}H and 75.429 MHz for ^{13}C. The nmr spectral parameters were read out from standard proton and carbon spectra with digital resolution of 0.2 Hz/point for ^{1}H and 1Hz/point for ^{13}C, respectively. The DQ-COSY and HETCOR spectra were acquired using standard pulse sequences supplied by the producer. Similarly, standard parameters and standard pulse sequences were used to obtain NOESY and 1D NOE difference spectra. The mixing period in the NOESY experiment was set to 0.5 second. The saturation period in the 1D NOE experiment was 5 seconds. During this period the multiplet of the selected proton was irradiated with a series of very weak line-selective pulses distributed over the whole multiplet to minimize the saturation of a neighbour resonance. Eight dummy scans were used to reach steady state conditions. The HMBC spectra were obtained on a Bruker Avance-300 spectrometer with a pulse sequence incorporating pulsed-field gradients for coherence pathway selection. The periods for creation and refocusing of relevant heteronuclear antiphase magnetization were set to 60 mseconds. Spectral windows in both dimensions were set according to actual windows observed in standard proton and carbon spectra; 512 increments were used in t_1 domain, giving 28.7 Hz/point resolution in F_1 domain. In the F_2 domain the resolution was 3.2 Hz/point. For each t_1 increment 16 dummy and 64 normal scans were acquired. Squared sine function was used to multiply FID before FT in both dimensions. All nmr spectra of compound **6aB** were obtained on a Bruker AC-400 spectrometer equipped with a dual ^{1}H/^{13}C probe and operating at 400.136 MHz for ^{1}H and 100.614 MHz for ^{13}C. The ^{1}H nmr spectral parameters were obtained from a resolution enhanced spectrum with digital resolution of 0.13 Hz/point. The ^{13}C chemical shifts were determined directly from standard spectra with digital resolution of 1.4 Hz/point. The AB and ABX spin systems were analyzed using LAOCOON simulation program.

(6*R**,16*R**)-9,14-Dihydro-6-methyl-6,16-methano-6*H*,16*H*-[2,4]benzothiazepino[3,4-*d*][1,3,5]benzoxadiazocine Hydrobromide (**4**).

A solution of **1a** (1.0 g, 3.59 mmoles) and 1,2-bis(bromomethyl)-benzene (1.10 g, 4.2 mmoles) in commercial dimethylformamide (15 ml) was refluxed for 45 minutes. Evaporation of the solvent gave an oily residue which was thoroughly triturated with hot acetone. The solid obtained was collected, washed with acetone and air-dried to yield 0.93 g (64 %) of **4**, mp 237-238° dec (acetonitrile); ir (potassium bromide): ν 3431, 3120, 2939, 1584, 1535, 1116 cm^{-1}; ms: (EI) m/z (relative intensity) 322 (M^+, $C_{19}H_{18}N_2OS$, 26), 289 ($C_{19}H_{17}N_2O$, M^+ - SH, 45), 229 ($C_{13}H_{13}N_2S$, M^+ - C_6H_5O, 62), 145 ($C_{10}H_9O$, 100), 135 (C_8H_7S, 61), 115 (23), 104 (31), 95 ($C_5H_7N_2$, 46), 91 (33), 78 (21), 77 (22).

Anal. Calcd. for $C_{19}H_{19}BrN_2OS$: C, 56.58; H, 4.75; N, 6.95. Found: C, 56.39; H, 5.06; N, 6.71.

(6*R**,13*S**,19*S**,26*R**)-11,24-Dihydro-6,19-dimethyl-6,26:13,19-dimethano-6*H*,9*H*,13*H*,19*H*,22*H*,26*H*-benzo[1",2":5,6;4",5":5',6']-bis[1,3]thiazepino[2,3-*d*:2',3'-*d*']bis[1,3,5]benzoxadiazocine Dihydrobromide (**6aB**).

A solution of **1a** (1.11 g, 4.0 mmoles) and 1,2,4,5-tetrakis(bromomethyl)benzene (0.90 g, 2 mmoles) in commercial dimethylformamide (35 ml) was refluxed with stirring for 40 minutes. Formation of the precipitate began after 25 minutes. The reaction mixture was cooled to room temperature, the solid which separated was filtered by suction and washed with ethanol and then with acetone. The yield of **6aB** was 0.30 g (20 %), mp >300° dec (dimethylformamide/ethanol); ir (potassium bromide): ν 3425, 3124, 2941, 1586, 1572, 1537, 1111 cm^{-1}; ms: (FAB) m/z 649 and 647 $(M + HBr + H)^+$, 567 $(M + H)^+$.

Anal. Calcd. for $C_{32}H_{32}Br_2N_4O_2S_2$: C, 52.75; H, 4.43; N, 7.69; S, 8.80. Found: C, 52.47; H, 4.70; N, 7.55; S, 8.56.

Acknowledgments.

We thank Dr. V. Hanus of the Heyrovsky Institute of Physical Chemistry and Electrochemistry, Prague, for measuring the mass spectra. We are indebted to Dr. K. L. Loening, Topterm, Columbus, OH, for his help with naming the new heterocyclic systems.

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