A Convenient Synthesis of 1,3,6-Dioxazocine, 1,3,7-Dioxazonine, 1,3,8-Dioxazecine and 1,3-Dioxa-6,10-diazadodecane

Krzysztof E. Krakowiak* and Barbara Kotelko

Institute of Technology and Chemistry of Drugs, School of Medicine,
90145 Lodz, Poland

Jerald S. Bradshaw* and N. Kent Dalley

Chemistry Department, Brigham Young University,
Provo, Utah 84602 USA

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A series of perhydro heterocycles of eight to ten ring members containing one nitrogen and two oxygen atoms has been prepared. These include four 1,3,6-dioxazocines, and 1,3,7-dioxazonine and one 1,3,8-dioxazecine. A twelve-membered ring containing two oxygen and two nitrogen atoms was also prepared. An X-ray structure of one of the 1,3,6-dioxazocines, **5**, was determined. This compound crystallized in the orthorhomic space group Pccn with a = 25.922(15)Å, b = 12.150(4)Å and C = 9.342(4)Å. Two of the 1,3,6-dioxazocines have the benzylidine acetal structure which will hydrolyze to give benzaldehyde.

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Introduction.

Polymembered saturated heterocycles with both nitrogen and oxygen atoms in the ring where the heteroatoms are separated by two or more methylene groups have important complexing, solvating and pharmacological properties [1-3]. Perhydro heterocycles containing nitrogen and oxygen atoms with eight or more ring members and with only one methylene group between nitrogen atoms or nitrogen and oxygen atoms are less well known [4-8]. There are only a few reports of dioxa heterocycles of eitht or nine-ring members where the two atoms are separated by a methylene group [9-14]. The 1,3,7-dioxazonine, 1,3,8-dioxazecine and 1,3-dioxa-6,10-diazacyclododecane systems have not been reported.

As a continuation of our research on the synthesis of new heterocycles containing oxygen and nitrogen atoms, we have now prepared various derivatives of perhydro-1,3,6-dioxazocine, **3-6**, (Figure 1), perhydro-1,3,7-dioxazonine **7**, perhydro-1,3,8-dioxazecine **8**, and 1,3,6,10-dioxadiazacyclododecane **9**. Compounds **5** and **6** are benzylidene acetals and will give benzaldehyde on acid hydrolysis. Recent work on antitumor activity of benzaldehyde suggests that benzylidene acetals provide a less toxic method for introducing benzaldehyde into tumor systems [15-18]. The main goal of our research is to devise a general method of producing multimembered, fully saturated, heterocycles in which oxygens atoms are linked by a methylene or benzylidene bridge. These compounds could have antitumor activity.

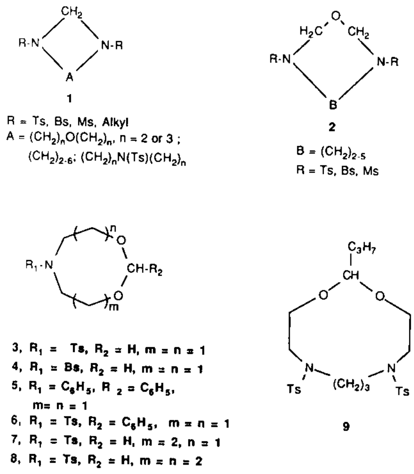
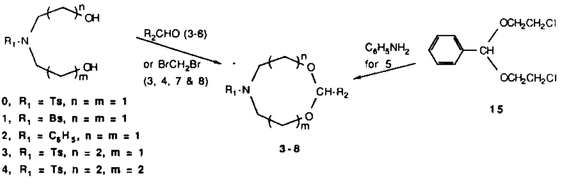


Figure 1. Structures Of Compounds

Results and Discussion.

1,3,6-Dioxazocines **3-6** were prepared by reacting the appropriate *N*-substituted diethanolamine with a dibromide or aldehyde or reacting aniline with the *bis*(2-chloroethoxy)acetal of benzaldehyde **(15)** to form **5** as shown in Scheme I. The reactions to form **3** and **4** using dibromomethane were superior to those using formaldehyde because, in the latter case, the crude products contained many materials and isolation of a pure **3** or **4** was very difficult. The first sequence is similar to that reported by Nishiyama and co-worker who reacted aldehydes or ketones with *N,N-bis*(2-hydroxyethyl)- or (2-hydroxypropyl)aniline containing electron withdrawing groups to prepare the 1,3,6-dioxazocines [10-13]. Compounds similar to **15** were used by us for the preparation of macrocyclic acetals [19]. The reaction of **15** with aniline in acetonitrile, using sodium carbonate as the base, gave a poor yield of **5**. On the other hand, both **5** and **6** were obtained in good yields by condensing benzaldehyde dimethyl acetal with the appropriate *bis*-ethanolamine in the presence of *p*-tol-

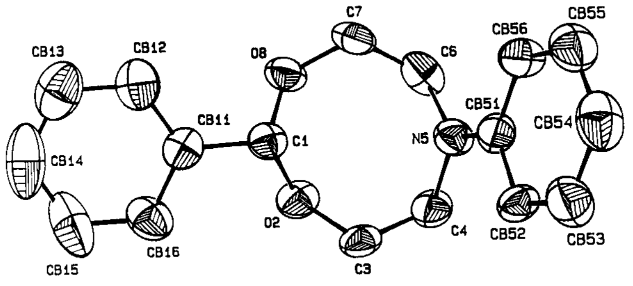

Scheme I. Preparation of New Cyclic Compounds

uenesulfonic acid in toluene or chloroform. The reaction to form **5** also gave 7-hydroxy-1-methoxy-1,5-diphenyl-2-oxa-5-azaheptane. It is interesting to note that *N*-benzyl-*bis*(ethanolamine) does not react with benzaldehyde dimethyl acetal to form the *N*-benzyl substituted 1,3,6-dioxazocine. Thus, it is apparent that a tosyl or phenyl (or substituted phenyl) group is needed on the *bis*(ethanolamine) substrate [11-14].

Compounds **7** and **8** were prepared from dibromomethane and the appropriate diol using cesium carbonate as the base. Kellogg and his co-workers have found that cesium salts were superior catalysts for ring closure in the preparation of macrocyclic compounds [20-21]. Compound **9** was prepared by reacting *N*,*N'*-ditosyl-1,3-diaminopropane with 1,1-*bis*(2-chloroethoxy)butane in dimethylformamide using potassium **t**-butoxide as the base.

The structures of all new heterocycles are consistent with data obtained from nmr and ir spectra, molecular weight and combustion analyses. A crystal structure determination (see below) was also done for **5**. The nmr spectra for **3**, **4**, **7** and **8** contained a singlet signal at δ 4.8 ± 0.1 indicative of the two acetal protons. The benzaldehyde acetal proton of **5** and **6** gave a signal at δ 5.58 ± 0.02.

Figure 2. Computer Drawing of Compound 5



An X-ray structural study of **5** was initiated in order to determine the conformation of the molecule. A computer drawing of the solid state structure is shown in Figure 2. The cavity of the eight-membered ring is too small to contain a metal ion. The bond lengths and angles for the atoms in the heterocyclic ring are given in Table I. The rather short CB51-N5 bond length and the fact that the sum of the angles about N5 is 359.1°, suggest a partial double bond character for the CB51-N5 bond. This is supported by the fact that the dihedral angle between a least square plane containing CB51, N5, C4, and C6 and the plane of the CB51 phenyl group is 6.3°. This rather rigid group, C4-N5-C6, likely causes enough strain in the eitht-membered ring so that several of the angles involving the non-hydrogen atoms of the eight-membered ring are larger than expected (see Table I).

Table I

Bond Lengths and Angles for **5** [a]

1	2	3	1-2(Å)	1-2-3(deg)
C1	O2	C3	1.422(7)	118.2(4)
O2	C3	C4	1.435(7)	112.2(5)
C3	C4	N5	1.491(9)	114.6(5)
C4	N5	C6	1.472(8)	116.8(5)
CB51	N5	C4	1.406(6)	120.3(4)
CB51	N5	C6	1.406(6)	122.0(5)
N5	C6	C7	1.447(8)	115.7(5)
C6	C7	O8	1.511(10)	115.4(5)
C7	O8	C1	1.426(8)	116.9(5)
O8	C1	C2	1.415(7)	109.7(5)
CB11	C1	O2	1.496(7)	108.8(5)
CB11	C1	O8	1.496(7)	108.9(5)

[a] C-C bonds in phenyl groups set at 1.395 Å and C-C-C angles in phenyl groups set at 120°.

Table II

Crystal and Experimental Data for **5**

Formula	$C_{17}H_{19}NO_2$
Formula weight	269.3
F(000)	1152
Crystal size, mm	0.4 x 0.4 x 0.3
Space group	Pccn
a, Å	25.921(12)
b, Å	12.145(3)
c, Å	9.334(3)
V, Å^3	2939(2)
Z	8
μ, cm^{-1}	0.74
dx, g/cc	1.22
R	0.079
Rw	0.089
Goodness of fit	1.17
largest peaks in Δ map	0.25, −0.27

Cycles **5** and **6**, which contain the benzylidene group as part of the ring, are currently being tested for anti tumor-activity.

EXPERIMENTAL

Infrared (ir) spectra were obtained on a Unicam SPP-200G infrared spectrometer in potassium bromide. The proton nuclear magnetic resonance (nmr) spectra were obtained on a Joel FX-90 Q or on a Varian EM-360 spectrometer. Molecular weights were determined by the elec-

Table III

Positional and Thermal Parameters for non-hydrogen Atoms of **5**

atom	x	y	z	U(Å^2) [a]
C1	0.4145(2)	0.0958(5)	0.5244(6)	0.045(2)
O2	0.3984(2)	0.2024(3)	0.4799(4)	0.053(2)
C3	0.3847(3)	0.2179(5)	0.3323(7)	0.052(3)
C4	0.3286(2)	0.1994(5)	0.3063(7)	0.056(3)
N5	0.3121(2)	0.0838(4)	0.3170(5)	0.048(2)
C6	0.2972(2)	0.0448(6)	0.4576(7)	0.059(3)
C7	0.3381(3)	−0.0184(5)	0.5387(7)	0.063(3)
O8	0.3757(2)	0.0472(4)	0.6104(4)	0.056(2)
CB11	0.4628(2)	0.1068(4)	0.6110(5)	0.046(2)
CB12	0.4734 [b]	0.0298	0.7180	0.065(3)
CB13	0.5183	0.0391	0.7994	0.084(4)
CB14	0.5526	0.1253	0.7738	0.102(4)
CB15	0.5420	0.2023	0.6668	0.097(4)
CB16	0.4971	0.1930	0.5854	0.066(3)
CB51	0.3190(2)	0.0117(3)	0.2008(3)	0.043(2)
CB52	0.3416	0.0484	0.0737	0.044(2)
CB53	0.3469	−0.0235	−0.0419	0.060(3)
CB54	0.3298	−0.1320	−0.0305	0.062(3)
CB55	0.3073	−0.1687	0.0966	0.060(3)
CB56	0.3019	−0.0968	0.2122	0.051(2)

[a] Equivalent isotropic U defined as one-third of the trace of the orthogonalized Uij tensor. [b] e.s.d. values for the rigid phenyl group atoms are identical to those values of the first atom of the group.

tron impact method on Finnegan 8430 or LKB 2091 high resolution mass spectrometers. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Starting materials were purchased from commercial sources where available. Starting *N*-tosyl-*bis*(2-hydroxyethyl)amine (**10**, see Scheme I) was prepared as reported [22]. *N*-Benzenesulfonyl-*bis*(2-hydroxyethyl)amine (**11**) [23], 2-hydroxyethyl-3-hydroxypropylamine [24] and *bis*(3-hydroxypropyl)amine [25] [nmr: (δ) 1.6-2.0 (m, 4H), 2.6-2.9 (t, 4H), 3.4-3.8 (t, 4H), 4.1-4.3 (s, 3H)] were prepared as reported. Benzaldehyde *bis*(2-chloroethoxy)acetal **15** was prepared according to our method [19]; nmr: (δ) 3.8 (m, 8H), 5.63 (s, 1H), 7.42 (m, 5H); ir: 1470 , 1420, 1400, 1340, 1320, 1270, 1170 cm^{-1}. Other starting materials were prepared as follows.

N-Tosyl-(2-hydroxyethyl-3-hydroxypropyl)amine (**13**) and *N*-Tosyl-*bis*(3-hydroxypropyl)amine (**14**).

To 10 g (0.075 mole) of *bis*(3-hydroxypropyl)amine or 8.9 g (0.075 mole) of (2-hydroxyethyl-3-hydroxypropyl)amine was added a solution of 8.0 g (0.075 mole) of sodium carbonate in 250 ml of water and 14.6 g (0.075 mole) of tosyl chloride. The mixture was heated at 95° for 1 hour and then left 2 hours at 25°. The water was evaporated to about 50 ml and extracted twice with 50 ml portions of chloroform. The chloroform extract was dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to yield 86% and 85% of **13** and **14** as oils. The spectra for **13** are as follows: nmr: (δ) 1.6-2.0 (m, 2H), 2.4 (s, 3H), 3.1-3.4 (m, 4H), 3.6-3.9 (m, 6H), 7.2-7.8 (dd, 4H); ir: 1160, 1340, 3400 cm^{-1}. The spectra for **14** are as follows: nmr: (δ): 1.5-2.0 (m, 4H), 2.4 (s, 3H), 2.6 (s, 2H), 3.1-3.3 (t, 4H), 3.6-3.8 (t, 4H), 7.2-7.8 (dd, 4H); ir: 1160, 1345, 3450 cm^{-1}. Combustion analyses were not carried out for **13** and **14**, however, the analyses for rings prepared from these materials were satisfactory.

Synthesis of 6-Tosylperhydro-1,3,6-dioxazocine (**3**).

N-Tosyl-*bis*(2-hydroxyethyl)amine **10** (2.07 g, 0.008 mole) was dissolved in 100 ml of methanol and 3.3 g (0.016 mole) of a 25% solution of sodium methoxide in methanol was added. (Identical results were obtained when 1.8 g (0.016 mole) of potassium *t*-butoxide was used instead of sodium methoxide.) The mixture was refluxed for 20 minutes and the solvent was evaporated under reduced pressure. The residue was added to 100 ml of DMF. Dibromomethane (1.33 g, 0.005 mole) in 90 ml of DMF was slowly added and the mixture was heated for 10 hours. The mixture was then evaporated and the residue was chromatographed on silica gel using chloroform:ethyl acetate (9:1) as eluant to give **3** (51%), mp 111-113°; nmr (deuteriochloroform): (δ) 2.4 (s, 3H), 3.3-3.5 (t, 4H), 3.7-4.0 (t, 4H), 4.8 (s, 2H), 7.2-7.8 (dd, 4H); ir: 1120, 1170, 1340 cm^{-1}; ms: (15 eV) 271 (8.6), 241 (17.8), 198 (23.6), 197 (61.8), 184 (56.8), 133 (16), 116 (100).

Anal. Calcd. for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.27; N, 5.17; S, 11.8. Found: C, 53.2; H, 6.3; N, 5.2; S, 11.7.

Synthesis of 6-(Benzenesulfonyl)perhydro-1,3,6-dioxazocine (**4**).

Compound **4** was prepared as above for **3** except 1.95 g (0.008 mole) of *N*-benzenesulfonyl-*bis*(2-hydroxyethyl)amine **11** was used. The crude product was chromatographed on silica gel (dichloromethane:ethyl acetate-8:1) to give **4** (55%) mp 52-54°; nmr: (δ) 3.3-3.5 (t, 4H), 3.6-3.9 (t, 4H), 4.75 (s, 2H), 7.4-7.9 (m, 5H); ir: 1120, 1170, 1340 cm^{-1}.

Anal. Calcd. for $C_{11}H_{15}NO_4S$: C, 51.97; H, 5.84; N, 5.45. Found: C, 51.8; H, 5.7; N, 5.6.

Synthesis of 2,6-Diphenylperhydro-1,3,6-dioxazocine (**5**).

A solution of 3.62 g (0.02 mole) of *N*-phenyldiethanolamine **12**, 3.04 g (0.02 mole) of benzaldehyde dimethyl acetal and a catalytic amount *p*-toluenesulfonic acid were dissolved in 200 ml of benzene. The benzene solution was heated to about 65° for 10 hours to allow some methanol and benzene to distill. Dry benzene was added periodically to the reaction flask. The remaining benzene was then evaporated to yield an oil which was chromatographed on silica gel (hexane: methylene chloride-60:40). Compound **5** (66%) was recrystallized from hexane, mp 103°; nmr: (δ) 3.7-4.1 (m, 8H), 5.6 (s, 1H), 6.7 (m, 2H), 7.4 (m, 8H).

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 76.36; H, 6.41. Found: C, 76.38; H, 6.68.

A second compound, 7-hydroxy-1,5-diphenyl-1-methoxy-2,5-oxaazaheptane, was also isolated; nmr: (δ) 2.0 (t, 1H, 2.12 (s, 3H), 2.7 (m, 8H), 5.5 (s, 1H), 6.76 (m, 3H), 7.40 (m, 7H); ir: 3400, 1570, 1470, 720, 670 cm^{-1}. This material was not further purified.

Synthesis of 2-Phenyl-6-tosylperhydro-1,3,6-dioxazocine (**6**).

A solution of 2.59 g (0.01 mole) of *N*-tosyldiethanolamine and 1.52 g (0.01 mole) of benzaldehyde dimethyl acetal and a catalytic amount *p*-toluenesulfonic acid in 400 ml of chloroform was refluxed using a Dean-Stark apparatus for 10 hours to allow some of the methanol to be removed. Chloroform was added periodically to the reaction flask. The solvents were then evaporated and the residue was chromatographed on silica gel (dichloromethane) to give 64% of **6** (recrystallized from hexane), mp 100°; nmr: (δ) 2.44 (s, 3H), 3.48 (t, 4H), 3.90 (m, 4H), 5.72 (s, 1H), 7.22-7.80 (m, 9H).

Anal. Calcd. for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09. Found: C, 62.26; H, 6.05.

Synthesis of 7-Tosylperhydro-1,3,6-dioxazonine (**7**).

A mixture of 2.73 g (0.01 mole) of *N*-tosyl-(2-hydroxyethyl-3-hydroxypropyl)amine (**13**), 100 ml of methanol, 4.5 g of a 25% solution of sodium methoxide in methanol and a trace of cesium carbonate was refluxed for 20 minutes. (Similar results were obtained when 2.25 g of potassium *t*-butoxide was used instead of sodium methoxide.) The solvent was completely removed and the residue was dissolved in 180 ml of DMF. The solution was heated to 80° and 2.0 g (0.01 mole) of dibromomethane in 50 ml of DMF was slowly added over a 3 hour period. The resulting mixture was stirred at 80° for 10 hours. The solvent was then evaporated under reduced pressure and the residue was chromatographed on a silica gel column using chloroform-ethyl acetate (1:1) as eluant to give a 42% yield of **7**, mp 96-98°; nmr: (δ) 1.8-2.1 (m, 2H), 2.4 (s, 3H), 3.2-3.5 (m, 4H), 3.8-4.0 (m, 4H), 4.8 (s, 2H), 7.2-7.8 (dd, 4H); ir: 1100, 1120, 1170, 1340, 2950 cm^{-1}; ms: (15 eV) 286 (M^+), 285, 256, 240, 184, 155, 130.

Anal. Calcd. for $C_{13}H_{19}NO_4S$: C, 54.73; H, 6.67; N, 4.91. Found: C, 54.60; H, 6.51; N, 4.83.

Synthesis of 8-Tosylperhydro-1,3,8-dioxazecine (**8**).

Compound **8** was prepared as above for **7** except 2.89 g (0.01 mole) of *N*-tosyl-*bis*(3-hydroxypropyl)amine (**14**) was used instead of **13**. Product **8** was isolated as a viscous oil, 32% yield; nmr: (δ) 1.8-2.2 (m, 4H), 2.4 (s, 3H), 3.2-3.5 (m, 4H), 3.8-4.0 (m, 4H), 4.8 (s, 2H), 7.2-7.8 (m, 4H); ms: (15 eV) 298, 270 (100), 240, 198, 188, 155, 142, 91, 70.

Anal. Calcd. for $C_{14}H_{21}NO_4S$: C, 56.19; H, 7.02; N, 4.68. Found: C, 56.38; H, 7.19; N, 4.81.

Synthesis 1,3-Dioxa-6,10-diazododecane (**9**).

To a mixture of 3.76 g (0.01 mole) of *N,N'*-ditosyl-1,3-diaminopropane in 250 ml of DMF and 2.5 g of potassium *t*-butoxide was added dropwise, 2.17 g (0.01 mole) of butyraldehyde *bis*(2-chloroethyl) acetal in 50 ml of DMF over a 5 hour period at 100°. The mixture was heated for 5 hours at 110° and evaporated under vacuum. The residue was dissolved in 20 ml of water and extracted twice with 100 ml portions of chloroform. The combined extracts were dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was chromatographed on silica gel using chloroform-ethyl acetate (15:1) as eluant to give 2 g (60%) of **9**, as an oil; nmr: (δ) 0.85 (m, 3H), 1.4 (m, 6H), 2.15 (s, 6H), 3.1 (m, 8H), 3.7 (t, 4H), 4.45 (t, 1H), 7.16-7.68 (dd, 8H); ir: 1580, 1440, 1340, 800 cm^{-1}; ms: 524, 369, 293, 239, 198, 85, 83.

Anal. Calcd. for $C_{25}H_{36}N_2O_6S_2 \cdot H_2O$: C, 55.33; H, 7.05. Found: C, 54.97; H, 6.81.

X-Ray Determination for **5**.

The crystals of **5** were of poor quality. This was evident from the fact that the Nicolet program for centering reflections failed to center many of the reflections selected for the lattice parameter determinations after seven interactions. Several crystals were evaluated for use in the study. The one chosen for data collection was satisfactory but had a large mosic spread. Crystal and intensity data were obtained using an automated Nicolet R3 diffractometer utilizing Mo Kα radiation (λ = 0.71073 Å). Lattice parameters were obtained using a least-squares procedure involving angle settings for 25 carefully centered reflections with $8.16° < 2\theta < 21.25°$. Because of the marginal quality of the crystal, it was not possible to find intense reflections on which to center beyond approximately $2\theta = 20$ degrees. This limited the accuracy of the lattice parameters which were determined to be a = 25.921(12)Å, b = 12.145(3)Å and c = 9.334(3)Å. The material crystallized in the orthorhombic space group Pccn with 8 molecules in the unit cell. A total of 2321 data were measured to a sin θ/λ limit of 0.54. These merged to 1938 unique data, 878 of which were considered unobserved ($F < 3\sigma(F)$). Crystal and experimental data are summarized in Table II. All non-hydrogen atoms were located in the initial E-map. Positions for hydrogen atoms were calculated based on geometric conditions. These hydrogens were assigned isotropic thermal parameters which were 1.2 times greater than the equivalent isotropic thermal parameters of the atoms to which they were bonded. Neither the positional nor the thermal parameters of the hydrogen atoms were refined. All hydrogen atoms bonded to the carbons of the eight-membered ring were allowed to ride on those carbon atoms. Non-hydrogen atoms were refined ansotropically. Weights based on counting statistics and an empirical extinction correction were applied to the data during the final stages of refinement. The final R values were R = 0.079 and Rw = 0.089. In the final refinement, seven additional weak reflections were considered unobserved for which the scans showed no intensity and the F calculated values were small but for which the F observed values were slightly greater than $3\sigma(F)$. The large number of weak reflections and the poor quality of the crystal partially account for the large R values. The rather large thermal parameters for the CB11 phenyl group suggest some disorder in the structure but it could not be resolved. This unresolved disorder would also contribute to larger R values. Positional and isotropic thermal parameters for the non-hydrogen atoms are listed in Table III. All calculations were made using SHELXTL [26], a program package supplied by Nicolet. Atomic scattering factors were obtained from Volume IV of the International Tables for X-ray Crystallography [27].

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