The Configuration and Solid State Conformation of 3,7-Dihydroxy-1,5-bis(*p*-bromophenyl)octahydro-1,5-diazocine

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The crystal structure of 3,7-dihydroxy-1,5-bis(*p*-bromophenyl)octahydro-1,5-diazocine (**4**) has been determined from the three dimensional x-ray diffraction data. This infers a similar structure for 3,7-dihydroxy-1,5-diphenyloctahydro-1,5-diazocine (**1**). The molecules are in a twist crown conformation and the configuration of the hydroxyl groups on the 3,7-positions is *cis*.

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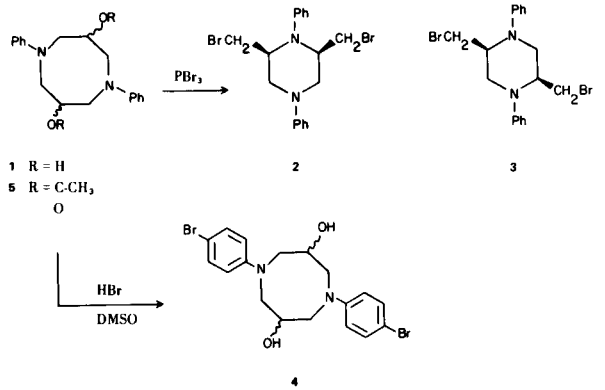
The chemistry of octahydro-1,5-diazocines has been of interest to several groups of workers for the past ten years (1,2). The ring system is unique because it undergoes a very facile ring contraction to yield substituted piperazines. Another interesting point is the fact that 3,7-dihydroxy-1,5-diphenyloctahydro-1,5-diazocine (**1**) prepared by the method of Gaertner (3) results as only one isomeric product. It was impossible to determine whether the 3,7-substituents were *cis* or *trans* using the common organic spectroscopic techniques. Upon reaction of **1** with



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phosphorus tribromide two isomeric piperazines were isolated (2). They were the *cis*-2,5- and *cis*-2,6-bromomethyl piperazines compounds, **2** and **3**. If one assumes a one or two nitrogen mechanism (see discussion) and the most stable conformation of the *cis* eight membered ring, it is possible using molecular models to predict the formation of only the *cis* piperazines from the *cis* configuration of **1**. It was imperative therefore that we determine unequivocally the configuration and conformation of **1**.

X-Ray data were taken on 3,7-dihydroxy-1,5-diphenyloctahydro-1,5-diazocine (**1**) but the structure could not be solved by routine techniques (4). A heavy atom substituent was deemed necessary to solve the structure. Compound **1** was reacted with hydrogen bromide in DMSO, to give a compound with bromines substituted exclusively on the *para* position of the phenyl ring (**4**) (5). This reaction in no way alters the configuration about the 3,7-positions and one can infer that the configuration of the dihydroxy compound **1** will be identical to that of compound **4**.

The crystal structure of **4** was determined from three dimensional x-ray data and is shown in Figures 1 and 2. The structure was solved by the method of symbolic addition and refined by block-matrix least squares analysis to an R value of 0.101. The molecule is in the twist crown conformation and close examination of Figures 1 and 2 along with molecular models establishes that the hydroxyl groups in the 3,7-positions are *cis* to one another.

The bond angles about the two nitrogen atoms indicate that the hybridization is approximately an sp^2 type leaving a nearly pure p orbital for the lone pair electrons. This is important because electrons in a p-orbital (versus any sp hybrid) are a greater distance from the nucleus making them more polarizable and therefore more nucleophilic. Figure 3 describes the ring contraction involving the lone pair electrons on nitrogen. The formation of *cis* 2,6- and *cis* 2,5-bromomethyl-1,4-diphenylpiperazines is dependent on the configuration of the 3,7-substituents on the eight membered ring. The *cis* diazocines, **1** and **4**, result in the formation of *cis* piperazines.

As expected the twist crown conformations of **1** and **4** place the 3,7-substituents in a *pseudo*-equatorial position thus minimizing atomic interactions. This conformation also allows for the ease of backside attack by the nitrogen lone pairs. Our speculation as to the configuration of **1** in our earlier work is now justified (2).

A molecule of ethanol crystallizes with each eight membered ring of **4**. The ethanol molecule is not shown in Figures 1 and 2 but the atom positions are given in Table III and IV as C(19) - C(20), O(3) and H(20) - H(21).

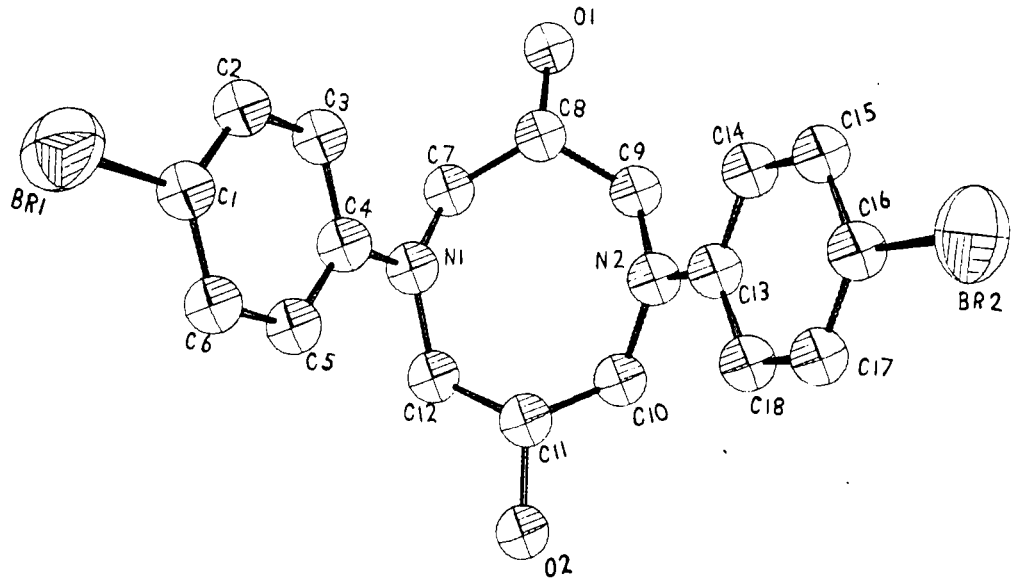

Figure 1. Top view of **4** showing the configuration of the hydroxyl groups O1 and O2 as extending back and down or *cis*.

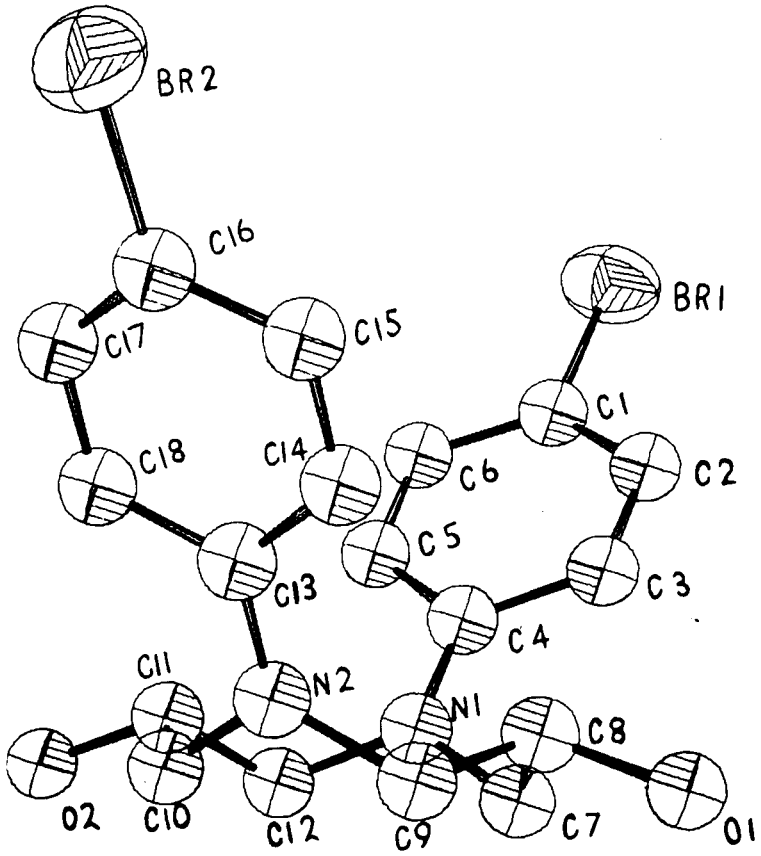

Figure 2. Side view of **4** showing the twist crown conformation and the configuration of the hydroxyl groups O1 and O2 as *cis*.

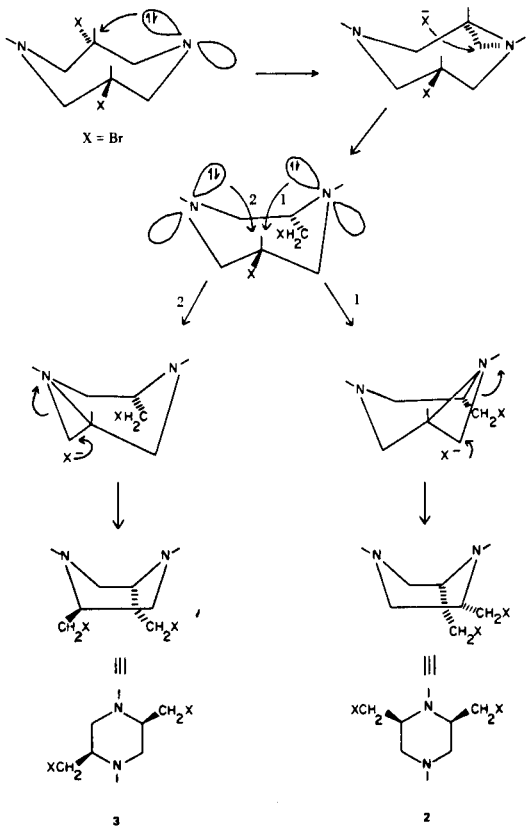

Figure 3. "One or Two Nitrogen Mechanism" for the formation of substituted piperazines **2** and **3** from substituted octahydrodiazocine **1**.

Table I

Fractional Atomic Coordinates of the Non-Hydrogen Atoms ($X10^4$)

Atom	X	Y	Z	Atom	X	Y	Z
Br1	313(2)	2029(2)	7094(1)	N1	3330(10)	7770(10)	7366(6)
Br2	8977(2)	1499(2)	110(1)	C7	3990(10)	7480(10)	6670(10)
Cl	1300(10)	720(10)	7190(10)	C8	5170(10)	8030(10)	6684(8)
C2	1920(10)	440(10)	6543(9)	O1	5508(9)	7960(7)	5848(5)
C3	2600(10)	9470(10)	6601(9)	C9	6140(10)	7430(10)	7246(8)
C4	2680(10)	8750(10)	7307(8)	N2	6080(10)	7680(9)	8147(6)
C5	2060(10)	9080(10)	7960(10)	C10	5480(10)	6920(10)	8627(9)
C6	1350(10)	40(20)	7909(9)	C11	4230(10)	7250(10)	8779(8)
O2	3880(10)	6570(10)	9446(6)	C17	7340(10)	-300(10)	9777(9)
C12	3270(10)	7000(10)	8062(8)	C18	6680(20)	8810(10)	9389(9)
C13	6710(10)	8580(10)	8531(7)	O3	7150(10)	9528(8)	5678(6)
C14	7390(10)	9300(10)	8096(8)	C19	8400(20)	9680(10)	5830(10)
C15	8060(10)	170(10)	8481(8)	C20	8970(20)	8590(20)	5790(10)
C16	8040(10)	340(10)	9337(8)				

Table II

Fractional Coordinates of the Hydrogen Atoms ($x10^3$)

Atom	X	Y	Z	Atom	X	Y	Z
H1	260(10)	80(10)	630(10)	H13	410(10)	690(10)	0(10)
H2	290(10)	930(10)	600(10)	H14	250(10)	700(10)	820(10)
H3	200(10)	880(10)	860(10)	H15	340(10)	620(10)	780(10)
H4	90(10)	0(10)	840(10)	H16	720(10)	940(10)	750(10)
H5	340(20)	690(10)	620(10)	H17	870(10)	70(10)	820(10)
H6	360(20)	760(10)	610(10)	H18	720(10)	0(10)	30(10)
H7	500(10)	880(10)	690(10)	H19	590(10)	850(10)	960(10)
H8	660(20)	810(10)	690(10)	H20	910(10)	0(10)	620(10)
H9	720(20)	740(10)	730(10)	H21	900(20)	10(20)	540(10)
H10	590(10)	750(10)	910(10)	H22	940(20)	880(10)	620(10)
H11	590(20)	690(10)	940(10)	H23	970(20)	850(10)	570(10)
H12	420(10)	800(10)	910(10)	H24	910(20)	850(10)	520(10)

The hydrogen atoms on the hydroxyl groups were not located but the ethanol oxygen atom appears to bond to both eight membered ring hydroxyl groups (O(1) - O(3) (2) Å and O(2) - O(3) on a different eight membered ring molecule 2.72 (2) Å).

In a final difference map no peak had an electron density greater than 0.75 electrons/Å (3).

An area of current investigation is the potential mechanistic control of ring contraction when the phenyl groups contain different electron withdrawing substituents.

The fact that there is stereospecific control in the preparation of **1** is also intriguing.

EXPERIMENTAL

Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. The ir spectra were obtained with a Perkin-Elmer 700 infrared spectrophotometer. The nmr spectra were obtained with a 60 MHz Varian A-60A spectrometer. Tetramethylsilane was used as an external standard. Elemental analysis was performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Preparation of 3,7-Dihydroxy-1,5-diphenyloctahydro-1,5-diazocine (**1**).

This compound was prepared by a modification, described elsewhere (2) of the method of Gaetner (3).

Preparation of 3,7-Dihydroxy-1,5-bis(*p*-bromophenyl)octahydro-1,5-diazocine (**4**).

To 1.0 g. of 3,7-dihydroxy-1,5-diphenyloctahydro-1,5-diazocine (**1**) in 50 ml. of dimethylsulfoxide was added 3.0 ml. of 48% hydrobromic acid. The reaction mixture was stirred at room temperature for 2 hours. The mixture was then added to 250 ml. of water. Sodium hydroxide (10% solution) was added until the solution was basic to litmus. After standing for 1 hour the solution was filtered by suction. The resulting off-white powder was recrystallized from methanol to give a white crystalline compound, yield 90%, m.p. 176-178°; ir (Nujol): 1600,

Table III

Selected Intramolecular Bond Lengths and their e.s.d.'s in A°

Br1 - C1	1.93(1)	C12 - N1	1.47(2)
C1 - C2	1.38(2)	C8 - O1	1.46(2)
C2 - C3	1.40(2)	C11 - O2	1.46(2)
C3 - C4	1.44(2)	C13 - N2	1.40(2)
C4 - C5	1.40(2)	C13 - C14	1.41(2)
C5 - C6	1.41(2)	C14 - C15	1.40(2)
C1 - C6	1.43(2)	C15 - C16	1.41(2)
C4 - N1	1.39(2)	C16 - Br2	1.91(1)
N1 - C7	1.48(2)	C16 - C17	1.37(2)
C7 - C8	1.49(2)	C17 - C18	1.41(2)
C8 - C9	1.53(2)	C13 - C18	1.43(2)
C9 - N2	1.51(2)	O3 - C19	1.42(2)
N2 - C10	1.43(2)	C19 - C20	1.47(3)
C10 - C11	1.52(2)		
C11 - C12	1.53(2)		

Table IV

Selected Intramolecular Bond Angles in Degrees

Br1 - C1 - C2	119(1)	C3 - C4 - C5	117(1)
Br1 - C1 - C6	120(1)	C3 - C4 - N1	123(1)
C2 - C1 - C6	121(1)	C5 - C4 - N1	120(1)
C1 - C2 - C3	119(1)	C4 - C5 - C6	122(1)
C2 - C3 - C4	123(1)	C1 - C6 - C5	119(1)
C4 - N1 - C7	118(1)	N1 - C12 - C11	112(1)
C4 - N1 - C12	121(1)	N2 - C13 - C14	122(1)
C7 - N1 - C12	121(1)	N2 - C13 - C18	121(1)
N1 - C7 - C8	115(1)	C14 - C13 - C18	117(1)
C7 - C8 - O1	107(1)	C13 - C14 - C15	122(1)
C7 - C8 - C9	112(1)	C14 - C15 - C16	119(1)
O1 - C8 - C9	106(1)	Br2 - C16 - C15	119.8(9)
C8 - C9 - N2	112(1)	Br2 - C16 - C17	119(1)
C9 - N2 - C10	119(1)	C15 - C16 - C17	121(1)
C9 - N2 - C13	120(1)	C16 - C17 - C18	120(1)
C10 - N2 - C13	120(1)	C13 - C18 - C17	121(1)
N2 - C10 - C11	116(1)	O3 - C19 - C20	108(1)
C10 - C11 - O2	109(1)		
C10 - C11 - C12	114(1)		
O2 - C11 - C12	103(1)		

1500, 1390, 1270, 1220, 1070, 850 and 810 cm^{-1}; nmr (DMSO-d_6): δ 6.5-7.3 (AA'BB', 8), 5.3 (m, 2H), 3.2-4.1 (m, 8H).

The structure was further proven by conversion to the diacetate and hydrolysis of the diacetate to give a compound identical with **4**.

Preparation of the 3,7-Diacetate of 3,7-dihydroxy-1,5-bis(*p*-bromophenyl)octahydro-1,5-diazocine (**5**).

Three g. of the bis(*p*-bromophenyl) dihydroxy compound, (**4**) were mixed with 1.5 g. of powdered sodium acetate and 15 ml. of acetic anhydride. The mixture was refluxed overnight and then added to 100 ml. of ice water. The resulting solid was filtered and recrystallized from methanol to give a white needle like compound, yield 70%, m.p. 233-235°; ir (Nujol): 1730, 1600, 1500, 1230, and 820 cm^{-1}; nmr (deuteriochloroform): δ 6.6-7.4 (AA'BB', 8), 5.1 (m, 2), 3.1-4.3 (ABX, 8) 2.2 δ (s, 6).

Anal. Calcd. for $C_{20}H_{24}Br_2N_2O_4$: C, 48.91; H, 4.48. Found: C, 48.74; H, 4.50.

The diacetate was hydrolyzed in dilute sodium hydroxide (10%) with stirring and gentle heating (80°) for 10 hours. The mixture was neutralized with dilute hydrochloric acid and filtered with suction. The solid obtained was recrystallized from methanol to give a compound identical in all respects to compound **4**.

X-Ray Data for Compound **4**.

The approximate cell dimensions of the crystal **4** used for data collection as well as the allignment of the crystal on the diffractometer were determined using the technique reported by Jacobson (6). The crystal was rod shaped with approximate dimensions of 0.2 x 0.6 x 0.3 mm. Using monochromated molybdenum radiation eleven reflections were centered at 2θ and -2θ and accurate lattice constants were determined using locally written programs.

Crystal Data: $C_{18}H_{20}Br_2N_2O_2 \cdot C_2H_6O$ M = 455.8, Monoclinic, a = 11.35 (4), b = 12.05 (4), c = 16.32 (7) Å, β = 97.2 (2)°, U = 2211.7 $Å^3$, D_M = 1.47, Z = 4, D_c = 1.52 g. cm^{-3}, space group = $P2_1/C$.

Peak top intensities corrected for background were measured for one quarter of the reciprocal sphere out to a 2θ cutoff of 40°. The radiation used was graphite monochromated MoKα (λ = 0.71069 Å). Standard deviations were obtained from counter statistics.

$$\sigma_I = C_T + C_B + (0.03\ C_T)^2 + (0.03\ C_B)^2$$

Reflections with $F < 3\sigma_F$ were not used in the refinement. No correction was made for adsorption (μ = 41.6 cm^{-1}) or dispersion.

A trial structure was developed from a preliminary data set using the program set MAGIC and LINK (7) in which the phases of 165 reflections were determined to be positive. The remainder of the structure was solved by normal least squares and electron density techniques. Near the end of the refinement an ethanol molecule was added to the model in the vicinity of one of the hydroxy groups. Non-hydrogen atomic scattering factors were those given by Hanson *et al.*, (8). Hydrogen atoms located on difference Fourier maps were included using isotropic thermal parameters.

The final residual of 0.101 was obtained for 719 reflections greater than 3σ (R_W = 0.121). A structure factor table is deposited as supplementary publication. Final parameters are given in Tables I and II, bond distances and angles are presented in Tables III and IV.

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