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The Effect of para-Substituents on the Conformational Behavior of 2,2-Diaryl-1,3-oxazine-4,6-diones: Evidence from a Crystal Structure Determination[1]

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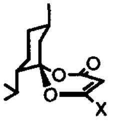
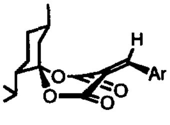
Summary: The crystal structure of 2,3-bis(4-methoxyphenyl)-2-(4-nitrophenyl)-1,3-oxazine-4,6-dione (**9**) was elucidated by X-ray structure analysis. This analysis has revealed two interesting characteristics: 1) The molecule is in a boat conformation with C(2) and C(5) pointing upward with angles of 41.9° and 26.0°, respectively and 2) The 4-nitrophenyl group takes a quasi-axial conformation.

The second characteristic can be interpreted in terms of stabilizing interaction between the lone pairs on N(3) and/or O(1) and the σ^*-orbital on the axial C(2)-aryl bond. The similar interaction of the lone pairs to π-orbitals of C(4 and 6)=O is also considered to account for the first characteristic.

Using spirocyclic dioxinones (**1**), dioxanediones (**2**), and oxazinediones (**3**), a series of methodologies for providing highly diastereoselective transformations has been elaborated in this[2] and other laboratories.[3] More recently, the corresponding heterocyclic compounds (2-monosubstituted[4,5] and 2,2-disubstituted derivatives:[6-8] e.g. **4**~**7**) were also synthesized and used successfully for the synthesis of a variety of EPCs (enantiomerically pure compounds). The common structural feature of these six-membered heterocyclic compounds which not only was verified from crystallographic analysis but also accounted for the observed diastereofacial selectivity is the sofa (**1**, **4**, **5**) or boat conformation (**2**, **3**, **6**, **7**) of the hetero rings with the acetal carbon out of the plane including at least four other atoms except



1: X=H, alkyl



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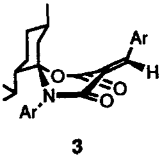

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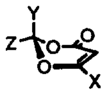
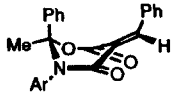


4: Y=H, X, Z=alkyl
5: Y=CO₂R, X=H, Z=Ph



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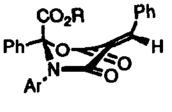

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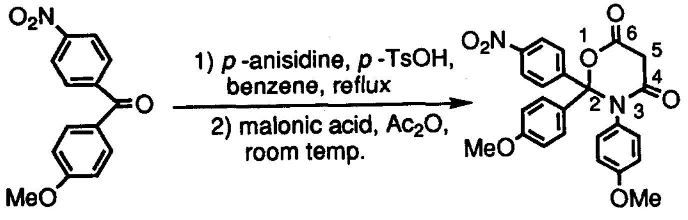
the one at the 5-position.

Since 2,3-bis(4-methoxyphenyl)-2-(4-nitrophenyl)-1,3-oxazine-4,6-dione (**9**) is obtained in crystalline form, it is possible to determine its structure by means of crystallographic analysis. Such a study would provide useful information for the origins of 1) the sofa and boat conformations of these hetero rings and 2) the conformations of their substituents at the 2-position.

According to the general synthetic method of 1,3-oxazine-4,6-dione derivatives,[9] the imine derived from 4-methoxy-4'-nitrobenzophenone[10] (**8**) and *p*-anisidine (reflux in benzene containing *p*-TsOH) was subjected to react with malonic acid in acetic anhydride (room temp.) to give the oxazinedione (**9**). Though usual silica gel column chromatography had failed due to instability of the product, the desired compound (**9**) was obtained when the chromatography was performed at a low temperature.[11]



8 **9**

A crystal of **9** ($C_{24}H_{20}N_2O_7$, mp 87-91 °C from acetone/hexane),[12] 0.4 x 0.3 x 0.3 mm in size, is triclinic with space group $P\bar{1}$, a=10.883(2) Å, b=13.968(2) Å, c=9.024(2) Å, α=105.40(2)°, β=100.01(2)° and γ=80.68(2)°. A single molecule of **9** and solvent molecule acetone with occupancy being 0.7 were found in each asymmetric unit to give a calculated density of 1.252 g/cm^3. Accurate unit cell constants were determined by a least-squares fitting method for the 40 high angle-reflections of angular range of $45° < 2\theta < 55°$. A total of 3326 reflections were collected on a Rigaku AFC-5R automated four-circle diffractometer with graphite-mono-chromated Cu Kα radiation (λ=1.54184 Å), of which 458 weak reflections below background were considered zero-reflections. The intensities were corrected for Lorentz and polarization factors, but not for absorption and second extinction.

The structure was solved by the direct method (SHELXS-86).[13] After all non-hydrogen atoms located from E maps were refined anisotropically with block-diagonal least-squares calculations, difference Fourier maps showed the presence of solvent molecule. These peaks were assigned to acetone and they were incorporated into the crystal lattice with occupancy being 0.7 so as to give a best R value. However, the other peaks located around acetone suggested disorder. After the anisotoropic stage of refinement had been reached, hydrogen atoms except for two methoxy groups were located on difference maps and refined isotoropically. The final R value was 0.078.

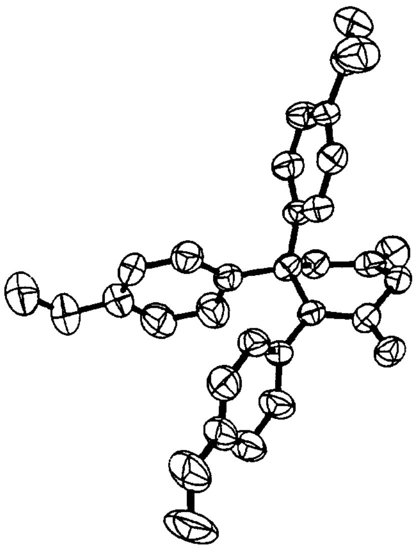


Figure 1. Perspective view of 9 (acetone molecule is omitted for simplicity)

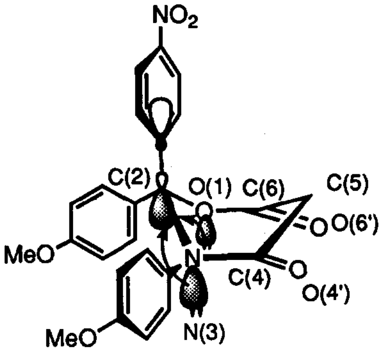


Figure 2. Perspective drawing of 9 with the atomic numbering

The conformation of the molecule and the atomic numbering are shown in Figures 1 and 2. The bond distances and angles are listed in Table 1. In Table 2 the distances of the 1,3-oxazine-4,6-dione ring (moiety) from the best plane through O(1)-N(3)-C(4)-C(6) are given. From this table it is seen that the oxazine ring is in a boat conformation with C(2) and C(5) pointing upward. C(2) and C(5) atoms are shifted 0.578 Å and 0.348 Å, respectively from the plane and also the planes through O(1)-C(2)-N(3) and C(4)-C(5)-C(6) make angles of 41.9° and 26.0° with the plane, respectively.

Table 1. Bond Distances and Bond Angles

===== Primary Atomic Distances (Å) =====

O(1)-C(2)	1.470(6)	O(1)-C(6)	1.356(6)	O(6')-C(6)	1.203(7)
O(4')-C(4)	1.211(6)	N(3)-C(2)	1.465(6)	N(3)-C(4)	1.356(6)
C(4)-C(5)	1.509(7)	C(5)-C(6)	1.464(7)		

===== Primary Valence Angles (Deg.) ======

C(2)-O(1)-C(6)	117.4(4)	O(1)-C(2)-N(3)	107.8(4)
C(2)-N(3)-C(4)	120.0(4)	N(3)-C(4)-C(5)	114.3(4)
C(4)-C(5)-C(6)	115.4(4)	O(1)-C(6)-C(5)	117.2(4)
O(1)-C(6)-O(6')	117.2(5)	N(3)-C(4)-O(4')	123.7(5)
C(5)-C(6)-O(6')	125.5(5)	C(5)-C(4)-O(4')	122.1(5)

Table 2. Distances (Å) from the Best Plane through O(1), N(3), C(4), and C(6)

O(1)	-0.0155	N(3)	0.0156	C(4)	-0.0147
C(6)	0.0146	C(2)	0.5780	C(5)	0.3477
O(4')	-0.3405	O(6')	-0.2713		

The molecular structure of **9** thus determined has revealed two interesting characteristics: 1) the molecule is in a boat conformation with C(2) and C(5) pointing upward and 2) the *p*-nitrophenyl group takes a quasi-axial conformation.

The conformation at the 2-position can be interpreted in terms of stabilizing interaction between the lone pairs on N(3) and/or O(1) with significant sp^3 character and the σ^* orbital on the axial C(2)-aryl bond. It is obvious that the overlap of the lone pair electrons on the heteroatoms to $\sigma^*_{p\text{-nitrophenyl(axial)-C(2)}}$ illustrated in Figure 2 should be important. A similar n/σ^* interactions between the lone pair electrons on these heteroatoms and the *p*-methoxyphenyl(axial)-C(2) bond in the hypothetical conformation whose two C(2)-aryl groups are reversed from **9** would be comparatively less important since the larger energy gap between the lone pair orbitals and $\sigma^*_{p\text{-methoxyphenyl-C(2)}}$. From purely energetic ground, the lone pair orbitals should be optimally a *p*-orbital. This stabilization leads to the fixing of *p*-nitrophenyl group in an axial conformation.[14]

Connection of the Newman projections along the O(1)-C(6) and N(3)-C(4) bonds of the actually observed boat conformation results in Figure 3-**a**. The nitrogen and/or oxygen lone pair p_z-orbitals are perpendicular to the plane of C(2)-N(3)-C(4) and/or C(2)-O(1)-C(6). From this figure, it is clear that the angles (α) between the p_z-orbitals (N and O) and the p_z-orbitals of C (4 and 6) are much smaller than the corresponding angles (α') of the hypothetical chair conformation

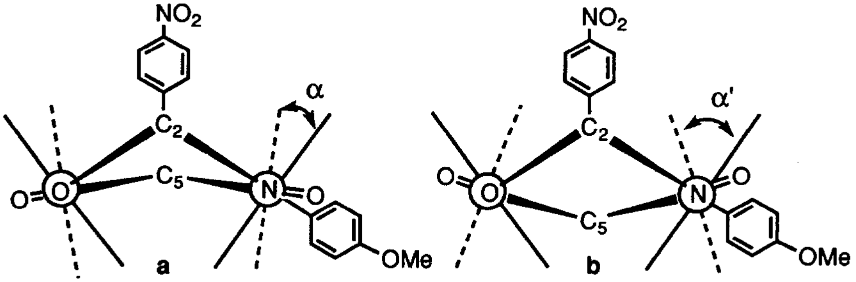


Figure 3. Newman projections along the O(1)-C(6) and the N(3)-C(4) bonds: closed lines, p_z-orbitals of O(1) and N(3); dotted lines, p_z-orbitals of C(6 and 4) in the C=O π-bonds.

(Figure 3-**b**). It is obvious that the boat conformation is more probable to attain the stabilizing interaction between the heteroatoms and the C-O π-bonds.[15]

In conclusion, we want to stress the point that the crystal structure determination of **9** as well as its reasoning presented in this paper would provide useful information predicting the conformation and facial selectivity of 1,3-dihetero six-menbered cyclic compounds (e.g. **1**~**7**).

Experimental Section

All melting points were determined on a micro-hot stage (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-102 spectrometer. ^{1}H-NMR spectra were recorded with a JEOL JNM PMX 60SI or a JEOL JNM-GX 500 spectrometer, with tetramethylsilane as an internal standard. Mass spectra (MS) were taken with a JEOL JMS 01SG-2 spectrometer. Silica gel used for column chromatography was Wakogel C-200 and the ratio of solvent mixtures is shown as volume/volume.

(±)-2,3-Bis(4-methoxyphenyl)-2-(4-nitrophenyl)-4,6-dioxotetrahydro-1,3-oxazine (9)

The synthesis of compound **9** was carried out through two steps (1: the imine formation from 4-methoxy-4'-nitrobenzophenone and *p*-anisidine and 2: the condensation of the imine with malonic acid).

Step 1. A solution of 4-methoxy-4'-nitrobenzophenone[10)] **8** (3.855 g, 15 mmol), *p*-anisidine (2.03 g, 16.5 mmol), and *p*-toluenesulfonic acid monohydrate (285 mg, 1.5 mmol) in benzene (100 ml) was refluxed for 1.5 days with azeotoropic removal of water. The solvent was evaporated off and the residue was chromatographed over silica gel (190 g) using benzene-hexane (4:1) to give yellow solid (2.935 g, 54%), which was recrystallized from a mixture of hexane and dichlorometane to give α-[(4-methoxyphenyl)imino]-α–4-nitrophenyl-4-methoxybenzene: yellow needles, mp 104-106 °C, High-resolution MS *m/z* Calcd for $C_{21}H_{18}N_2O_4$ (M^+): 362.1625. Found: 362.1623. IR ($CHCl_3$) 1610, 1520, 1515, 1505, 1350 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 3.67-3.80 (6H, m, OCH_3 x 2), 6.60-8.30 (12H, m, ArH).

Step 2. A mixture of malonic acid (468 mg, 4.5 mmol), the imine (1.107 g, 3 mmol), and acetic anhydride (12g, 0.115 mol) was stirrred at room temperature for 19 h. Most of acetic anhydride was evaporated off *in vacuo*. The residue was chromatographed over silica gel (25 g) using hexane-ethyl acetate (3:1) to give colorless oil,[11] which was crystallized from hexane at -25 °C and recrystallized from a mixture of acetone and hexane in a refrigerator.

9: pale yellow prisms, mp 87-91 °C (dec.). Anal. Calcd for $C_{24}H_{20}N_2O_7$: C, 63.30; H, 4.62; N, 6.42. Found: C, 63.17; H, 4.34; N, 6.44. IR ($CHCl_3$) 1780, 1735, 1700, 1610, 1530, 1515, 1370, 1350 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.454, 3.540 (each 1H, d, J=20.0 Hz, $C5H_2$), 3.692, 3.856 (each 3H, s, OCH_3), 6.768, 6.968 [each 2H, d, *J*=9.0 Hz, N-(4-CH_3O)C_6*H_4*], 6.652-6.970 [4H, m, C_2-(4-CH_3O)C_6*H_4*], 7.426, 8.034 (each 2H, *J*=9.0 Hz, 4-NO_2C_6*H_4*).

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11 The chromatography was performed by using silica gel column surrounded by an appropriate solvent cooled at -40 °C.

12 For the X-ray crystallographic analysis, the crystals of compound **9** were used as air dried specimen of recrystallized product. At this stage, the 500 MHz ^{1}H-NMR spectrum ($CDCl_3$) of the crystals showed δ 2.163 (s) corresponding to the methyl signals of acetone and δ 1.575 (broad s) of H_2O. After prolonged drying under vacuum, however, the former peak decreased.

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