On the Mechanism and Stereochemistry of the Formation of β-Lactam Derivatives of 2,4-Disubstituted-2,3-dihydro-benzo[1,4]diazepines

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2-Chloro-4-phenyl-2a-(4'-methoxyphenyl)-3,5-dihydroazatetracyclic[1,2-*d*]benzo[1,4]diazepin-1-one (**III$_a$**) and 2-chloro-4-methyl-2a-(4'-methoxyphenyl)-3,5-dihydroazatetracyclic[1,2-*d*]-benzo[1,4]diazepin-1-one (**III$_b$**) were synthesized. 1-Benzoyl-2-phenyl-4-(4'-methoxyphenyl)[1,4]-benzodiazepine (**II$_a$**) was formed through benzoylation of starting material 2-phenyl-4-(4'-methoxyphenyl)-[1,4]benzodiazepine (**I$_a$**) with the inversion of seven-member ring boat conformation. The thus formed β-lactams should have four pairs of stereoisomers. However, only one pair of enantiomers (2*S*,2a*R*,4*R*) and (2*R*,2a*S*,4*S*) was obtained. The mechanism and stereochemistry of the formation of these compounds were studied on the basis of nmr spectroscopy and further confirmed by X-ray diffraction.

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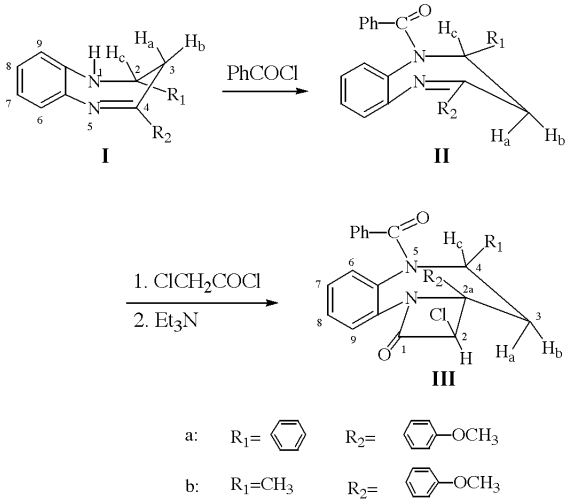
Diazepines are compounds showing high bioactivity, and studies on the synthesis of β-diazepine lactams have been reported [1,2]. However, there have been few reports so far on the mechanism and stereochemistry of the formation of diazepine β-lactams. In our previous study, a series of cycloaddition reactions of dihydrodiazepine and dihydrobenzothiazepine compounds were carried out, and interesting results obtained [3-7].

Scheme 1



Theoretically, the [2 + 2] cycloaddition reaction should give four pairs of β-lactam derivatives, but only one pair of diastereomers were obtained in the presence of triethylamine.

After thorough study on the reaction mechanism and the stereochemistry of both the starting material and the product, it was proposed that chloroacetyl chloride at first reacted with the imine functional group of 1-benzoyl-2-methyl(or phenyl)-4-(4'-methoxyphenyl)-benzo[1,4]diazepine (**II**) to give an unstable complex intermediate, followed by loss of a proton at the α position of the chloroacetyl group. A cycloaddition reaction then occurred after the intramolecular rearrangement of the intermediate. Alternatively, the reaction may have proceeded *via* stepwise [2 + 2] cycloaddition of the substrate with ketene, which was formed from chloroacetyl chloride by the action of triethyl amine present in the reaction mixture. The same intermediate, however, should be formed no matter which way the reaction proceeded. The ring closure step was governed by the conformation of both the intermediate and the product; the *R* product can only be formed through conrotatory counter-clockwise rotation (Scheme 2).

Results and Discussion.

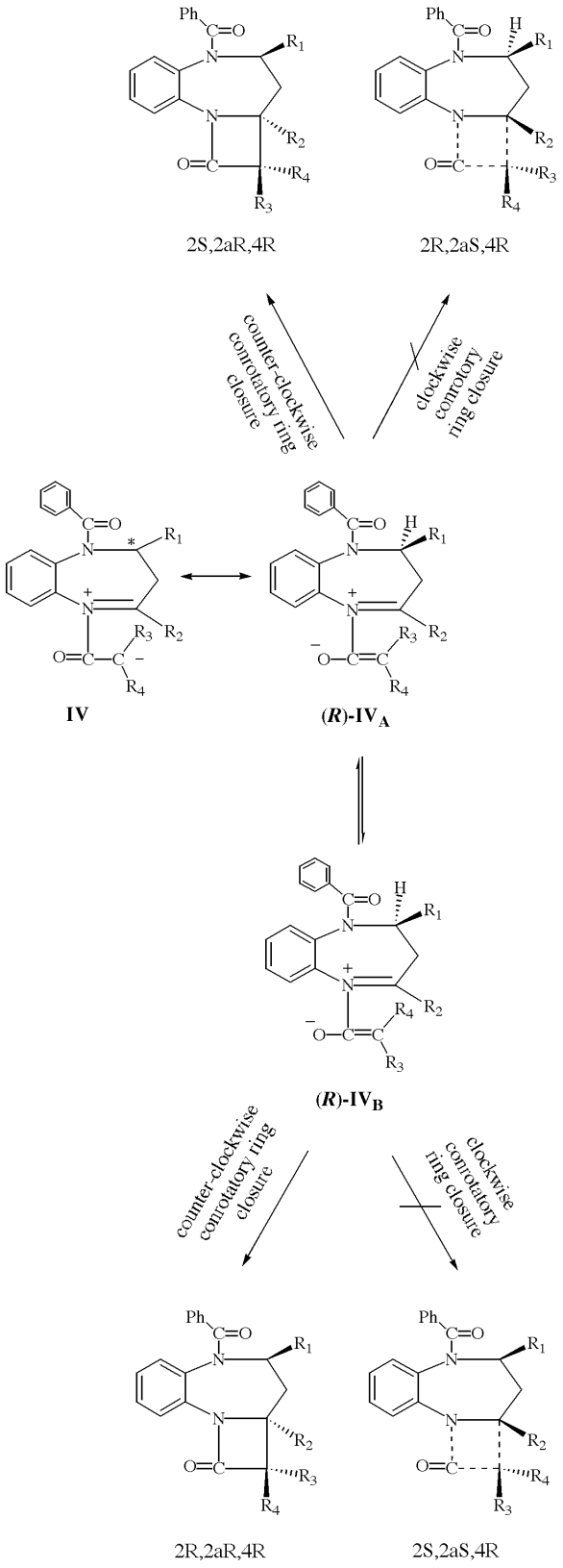
In order to facilitate the cycloaddition process, the N-H group in the starting material 2-phenyl-(or 2-methyl)-4-(4'-methoxyphenyl)-benzo[1,4]diazepine (**I**) was protected. A benzoyl group was used as the protective group, and nmr signals from the benzoylated product **II** differed significantly from those of the starting material **I**.

Table 1
Chemical Shifts and Coupling Constants of the Proton H_a, H_b and H_c on the Seven-member Ring of **I**, **II** and **III**

	H_a	H_b	H_c	J_{ab}	J_{ac}	J_{bc}
I$_a$	3.04	3.23	5.20	13.36	8.84	3.92
I$_b$	2.62	2.94	4.20	13.39	8.08	4.04
II$_a$	3.15	3.34	6.20	13.36	13.85	4.50
II$_b$	2.48	3.09	5.35	13.32	11.8	5.04

As shown in table 1, three protons on C-2 and C-3 of **I$_a$** form an AMX spin system, and show three quadruplets with coupling constants of J_{ab} = 13 Hz, J_{ac} = 9 Hz and J_{bc} = 4 Hz. After benzoylation, the coupling constants of these three protons are: J_{ab} = 13 Hz, J_{ac} = 14 and J_{bc} = 5 Hz.

Scheme 2



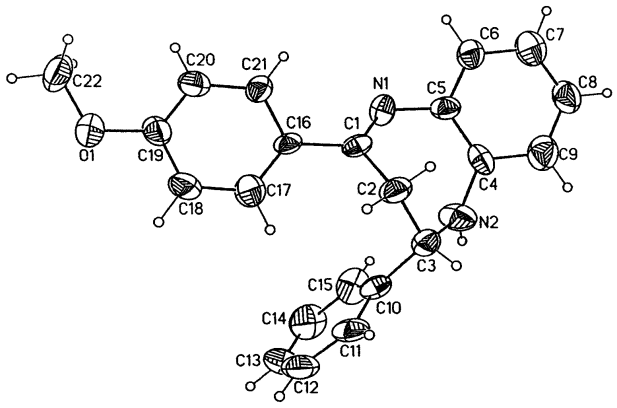


Figure 1. ORTEP drawing of compound $\mathbf{I_a}$.

According to the literature [8], proton H_c of $\mathbf{I_a}$ is in *+sc* relation with H_a and H_b and this has been changed after the benzoylation. In the benzoylated compound 1-benzoyl-2-phenyl-4-(4'-methoxyphenyl)-benzo[1,4]diazepine ($\mathbf{II_a}$), H_c and H_a are in *+ap* relation, while H_c and H_b are in a *+sc* relation. This means that the seven-member ring was inverted to a chair or boat conformation during the benzoylation process. The chair conformation is the high energy one, since the ring system contains a C=C double bond. Also, the benzoyl group and the neighboring phenyl group are in *+sp* relation, while the inversion to the boat

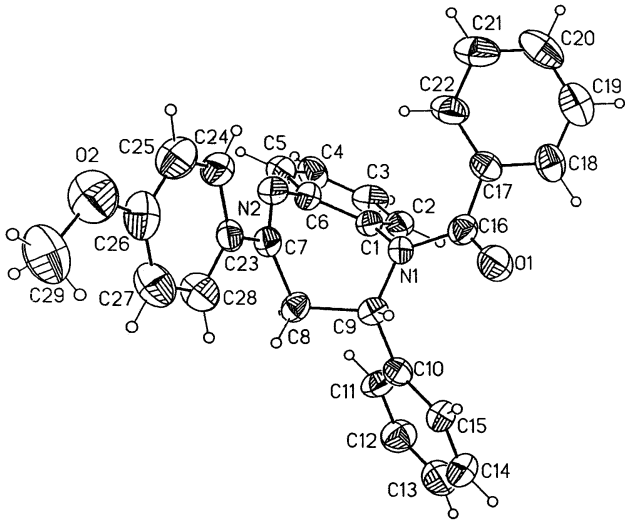


Figure 2. ORTEP drawing of compound $\mathbf{II_a}$.

conformation needs only a little energy [9]. In the boat conformation, the benzoyl group and the neighboring phenyl are in *+ap* relation. This was further confirmed by the X-ray crystal structure of compound $\mathbf{II_a}$.

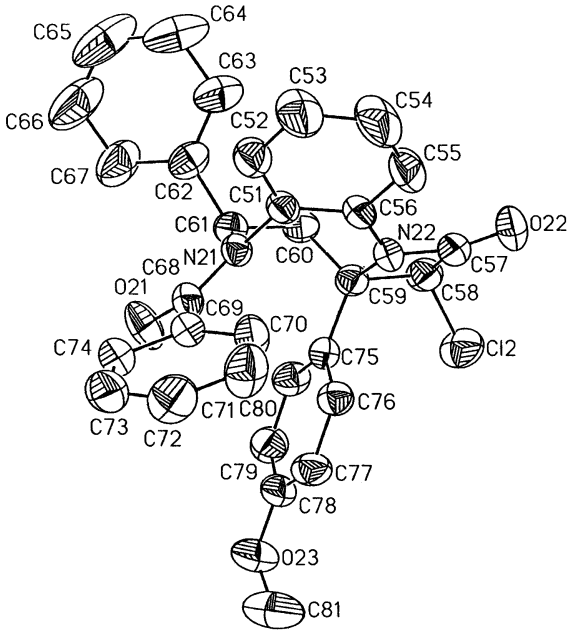


Figure 3. The ORTEP drawing of $\mathbf{III_a}$.

Szollozy *et al*. studied the stereochemistry of the formation of β-lactam derivatives *via* the reaction of benzo[1,4]thiazepine with ketene compounds bearing different substituents [10]. They usually obtained the (2*S**,2*aR**,4*R**) product as the only diastereomer. But when the α-substituents on the ketene have comparable size, another diastereomer (2*R**,2*aR**,4*R**) could also be obtained in small amount. They did not provide any explanation for this result. A previous study on the [2 + 1] cycloaddition of benzo[1,4]diazepine with ethoxy carbonyl carbene [11] showed that the factor governing the product stereochemistry was the conformation of the reaction intermediate. The [2 + 2] reaction seems to be a similar case. The chloroacetyl chloride or ketene molecule approaches the lone pair electron of the imine nitrogen atom from the less hindered direction, and the thus formed intermediate **IV** may have two conformations: $\mathbf{IV_A}$ or $\mathbf{IV_B}$. When R_3 = H and R_4 = Cl, $\mathbf{IV_A}$ is more stable than $\mathbf{IV_B}$. When undergoing 4π- cycloaddition reaction, there could be two different stereoisomers due to the rigidity and asymmetry of **IV**. (2*S*,2a*R*,4*R*) isomer will then be obtained when *R*-$\mathbf{IV_A}$ undergoes counter-clockwise conrotatory ring closure, while *S*-$\mathbf{IV_A}$ will give (2*R*,2a*S*,4*S*) isomer *via* clockwise conrotatory ring closure. And (2*R**,2*aS**,4*R**) isomers will be obtained when *R*-$\mathbf{IV_A}$ undergoes clockwise conrotatory and *S*-$\mathbf{IV_A}$ undergoes counter-clockwise conrotatory ring closure. Due to the rigidity and asymmetry of $\mathbf{II_a}$, the four-member ring of the (2*R**,2a*S**,4*R**) will reside perpendicular to the boat bottom of the seven-member ring. The N-5 benzoyl group will also reside at the boat bottom of the seven-member ring. This conformation has a high energy and is sterically hindered, and is thus difficult to form. However, $\mathbf{IV_B}$ may exist when R_3 and R_4 have comparable size, (2*R**,2a*R**,4*R**) diastereomers will be obtained when *R*-$\mathbf{IV_B}$ undergoes counter-clockwise conrotatory, and *S*-$\mathbf{IV_B}$ undergoes clockwise conrotatory ring closure. It is impossible to form the (2*S**,2a*S**,4*R**) diastereomer. This can then provide a reasonable explanation of Szollosy's two diastereomers that resulted from the reaction of O=C=C(Br)CH_3 with dihydrobenzo[1,4]thiazepine. The nmr spectrum of the mixture formed showed that two compounds were present. The major component was (2*S**,2a*R**,4*R**) and the minor one (2*R**,2a*R**,4*R**).

The related configurations of these compounds were further confirmed through X-ray diffraction studies of $\mathbf{I_a}$, $\mathbf{II}_a$ and 2-chloro-4-phenyl-2a-(4'-methoxyphenyl)-3,5-dihydro-azatetracyclic[1,2-*d*]benzo[1,4]diazepin-1-one ($\mathbf{III_a}$). The seven-member ring of $\mathbf{III_a}$ possessed a slightly twisted boat conformation with H_a and H_c in *sp* relation, while H_c and H_b were in +*sc* relation. The four-member ring of the β-lactam and the three atoms of the boat bottom remained co-planar. The methoxy group and benzoyl group were at the boat bottom, the phenyl group and the boat head resided on the same side, thus allowing the most favorable arrangement of the functional group (Figure 3).

EXPERIMENTAL

Melting points were measured on a Yanaco micro melting point apparatus and were uncorrected. Infrared spectra were recorded on Carlzearl Zeiss Jena Specord 75-IR instrument and ^{1}H nmr spectra on Brucker ARX-400 spectrometer using deuteriochloroform as solvent and tetramethylsilane as internal standard. Mass spectra were obtained on a VG ZAB-HS mass spectrometer. Microanalysis were carried out on a Perkin-Elmer 240C analyzer. X-ray diffraction data were obtained on a Rigaku AFC6S diffractometer. All solvents were dried and distilled before use.

4-(4-Methoxyphenyl)-2-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine ($\mathbf{I_a}$).

o-Phenylenediamine (18 g, 0.16 mmol) and 1-(4-Methoxy-phenyl)-3-phenylpropenone (38.1 g, 0.16 mmol) were dissolved in 225 ml of anhydrous ethanol. To this solution was added 5 ml of piperidine and the reaction mixture was refluxed for 9 hours. The reaction mixture was then concentrated and left standing to allow the crystallization of the product; 28 grams of yellowish solid was obtained in 77% yield, mp 102-4°; ir: ν 1605 (C=N) cm^{-1}.

Anal. Calcd. for $C_{17}H_{18}ON_2$ (266): C, 76.69; H, 6.77; N, 10.53. Found: C, 77.10; H, 6.90; N, 10.62.

4-(4-Methoxy-phenyl)-2-methyl-2,3-dihydro-1*H*-benzo[*b*][1,4]-diazepine ($\mathbf{I_b}$).

The reaction was carried out according to a procedure similar to that described for the preparation of $\mathbf{I_a}$. The product was received in 65% yield, mp 103-104°; ir: ν 3330, 1590 (C=N)

cm^{-1}; ms: m/z 328 (M$^+$, 80.2), 313(47.7), 224(100), 133(41.4); ^{1}H nmr (deuteriochloroform): δ 3.03 (dd, 1H), 3.22 (dd, 1H), 3.85 (s, 3H), 5.15 (dd, 1H), 6.84-7.87(m, 13H).

Anal. Calcd. for $C_{22}H_{20}ON_2$ (328): C, 80.49; H, 6.10; N, 8.54. Found: C, 80.62; H, 5.97; N, 8.43.

1-Benzoyl-4-(4-methoxyphenyl)-2-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine (**II$_a$**).

To a mixture of 17.0 g (0.054 mol) **I$_a$** and 7.5 ml triethyl amine in 260 ml of anhydrous benzene was added dropwise 6.8 ml (0.054 mol) of benzoyl chloride under reflux. The mixture was refluxed for another 6 hours after completing the addition, and then cooled and filtered to give 16.3 g of yellowish solid (yield 70%), mp 239-240° (ethanol). A single crystal suitable for X-ray diffraction analysis was obtained after recrystallizing twice from anhydrous ethanol. ir: 1640 (C=N) cm^{-1}; ms: m/z 432 (M$^+$, 23.4), 327 (62.0), 312 (10.9), 236 (10.7), 105 (100); ^{1}H nmr (deuteriochloroform): δ 3.15 (t, 1H), 3.33 (dd, 1H), 6.20 (dd, 1H), 6.66-8.13 (m, 18H).

Anal. Calcd. for $C_{29}H_{24}O_2N_2$ (432): C, 80.56; H, 5.56; N, 6.48. Found: C, 80.55; H, 5.39; N, 6.30.

1-Benzoyl-2-methyl-4-(4-methoxyphenyl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine (**II$_b$**).

The reaction was carried out using the procedure described above for the preparation of **II$_a$**. The product was isolated in 75% yield, mp 163-4°. A single crystal suitable for X-ray diffraction analysis was obtained after recrystallizing twice from anhydrous ethanol. ms: m/z 370 (M$^+$), 265, 251, 105 (100); ^{1}H nmr (deuteriochloroform): δ 1.40 (d,3H), 2.48 (t,1H), 3.09 (dd, 1H), 3.87 (s, 3H), 5.35 (m, 1H), 6.65-8.03 (m, 13H).

Anal. Calcd. for $C_{24}H_{22}O_2N_2$ (370): C, 77.84; H, 5.95; N, 7.57. Found: C, 77.83; H, 6.15; N, 7.53.

2-Chloro-4-phenyl-2a-(4-methoxyphenyl)-3,5-dihydroazetidino[1,2-*d*]benzo[*b*][1,4]diazepin-1-one (**III$_a$**).

To a solution containing 1.30 g (3 mmol) of **II$_a$** and 0.34 ml (6 mmol) of chloroacetyl chloride in 80 ml of anhydrous benzene was added a solution of 0.84 ml (6 mmol) triethylamine in 80 ml anhydrous benzene in 2 hours under reflux. The reaction mixture was then concentrated and separated *via* chromatography using cyclohexane:ethyl acetate (5:4) as the eluant to give 0.66 g of solid product in 43% yield, mp 224-5°; ir: ν 1770, 1630 cm^{-1}; ms: m/z 508 (M$^+$), 473, 427, 312, 105 (100), 77; ^{1}H nmr (deuteriochloroform): δ 2.90 (dd, 1H), 3.37 (dd, 1H), 3.72 (s, 3H), 5.03 (s, 1H), 6.10 (dd, 1H), 6.24-8.48 (m, 18H).

Anal. Calcd. for $C_{31}H_{25}O_3N_2Cl$ (508): C, 73.23; H, 4.92; N, 5.51. Found: C, 73.21; H, 4.76; N, 5.46.

2-Chloro-4-methyl-2a-(4-methoxyphenyl)-3,5-dihydroazatidino[1,2-*d*]benzo[*b*][1,4]diazepin-1-one (**III$_b$**).

The reaction was carried out by using the procedure described above for the synthesis of **III$_a$**; the product was isolated in 67% yield, mp: 236-7°. ir: ν 1760, 1620 cm^{-1}; ms: m/z 446 (M$^+$), 411, 265, 105 (100), 77; ^{1}H nmr (deuteriochloroform): δ 1.24 (d, 3H), 2.22 (dd, 1H), 3.24 (dd, 1H), 3.70 (s, 3H), 4.94 (s, 1H), 5.26 (m, 1H), 6.24-8.48 (m, 14H).

Anal. Calcd. for $C_{26}H_{23}O_3N_2Cl$ (446): C, 69.88; H, 5.15; N, 6.27. Found: C, 73.21; H, 5.22; N, 6.22.

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