A Study of the Reaction Between 2,4-Disubstituted-2,3-dihydro-1,5-benzothiazepines and Ketenes Generated *in situ* from Chloro and Dichloroacetyl Chlorides

Qi-yi Xing [a], Hong-zhong Wang* [a], Xin Zhou [a], Sheng Jin [a],
Yue-ming Li [b], and Albert S. C. Chan [b]

[a] School of Chemical and Molecular Engineering, Peking University,
Beijing 100871, People's Republic of China;
[b] Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University,
Hung Hom, Kowloon, Hong Kong, People's Republic of China
Received July 11, 2000

In the presence of triethyl amine, the reaction of 2,4-disubstituted-2,3-dihydro-1,5-benzothiazepine with chloro and dichloroacetyl chlorides produced not only the expected β-lactam derivative of the benzothiazepine, but also the ring opening product. Different results were obtained when the substituent at 2-position of the benxothiazepine varied from methyl to aryl, and the substituent on the chloroacetyl chloride varied from H to Cl, or when carrying out the reaction at different temperatures. The structures of the obtained products and the reaction mechanism are discussed.

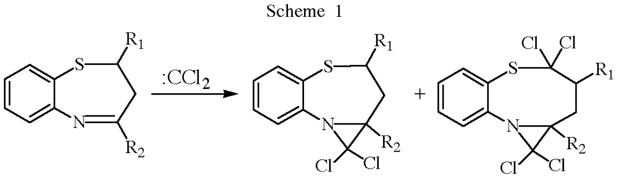
J. Heterocyclic Chem., **38**, 561 (2001).

Benzothiazepine compounds have demonstrated interesting bioactivity, and many papers discussing the synthesis, structure-property relationship and the application of such compounds have appeared [1]. It has been reported that compounds bearing benzothiazepine moieties have shown anti-HIV [2], anti-hypertensive [3], anti-depressant [4], and anti-bacterial activity [5]. For example, the drug diltiazem, which elicits anti-hypertensive effect, contains benzothiazepine as its structural subunit [6].

β-Lactam compounds also show high bioactivity and have been extensively studied [7]. It is therefore possible that compounds bearing both benzothiazepine and β-lactam moieties may display very interesting bioactivities. However, this possibility has not been thoroughly studied due mainly to the complexity of the reaction between 2,4-disubstituted-2,3-dihydro-1,5-benzothiazepine (**I**) and substituted acetyl chloride (**II**) [8]. A previous work in our group [9] has demonstrated that the reaction between **I** and **II** gave very different results depending on the substituents attached to the starting material **I**. Different reaction temperatures, or even the variation of the addition sequence for reagents, leads to very different results.

When the 2-position of **I** is a methyl group, the expected [2 + 1] product can be obtained from its reaction with dichlorocarbene. When R_1 is an aryl group, an unexpected eight-membered ring product is also formed, in addition to the expected three-membered ring product (Scheme 1) [10].

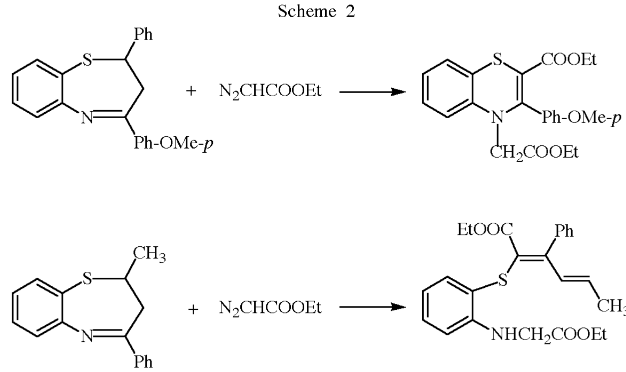
Scheme 1



R_1 = Ar

When reacting with ethoxycarbonylcarbene, benzothiazine bearing a 2-methyl or 2-aryl group also failed to give the expected [2 + 1] product (Scheme 2) [11-13].

Scheme 2

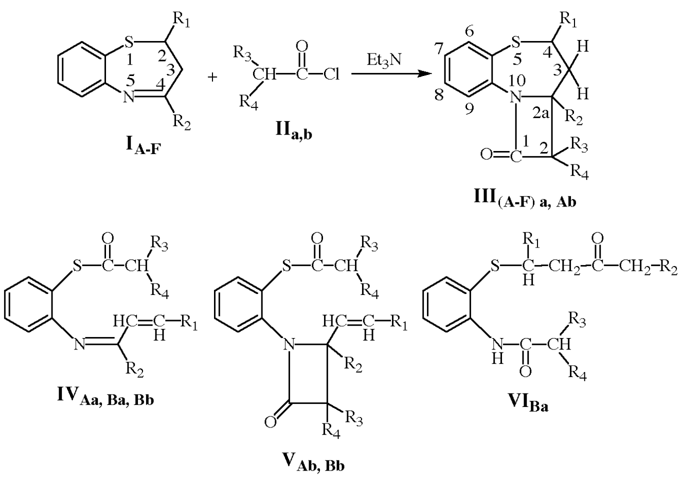


Previous publications in this area have left many factors affecting the reaction results unclear, particularly the 2-substituents of **I** and the substituents of **II**. Elucidating these effects was the primary objective of the present study.

Results and Discussion.

When subject to reaction in the presence of triethylamine, **I** and **II** showed different reactivity with different substituents on **I** or **II**, and several different products have been obtained. In our study, we also found different products were obtained at different reaction temperatures. When carried out at room temperature, reaction of **I** and **II** produced **III** as the major product, except that $\mathbf{V_{Bb}}$ was obtained as the major product in the reaction of 2-methyl substrate $\mathbf{I_B}$ with dichloroacetyl chloride. However, the reaction gave very complicated products when carried out at refluxed temperature, as reported in the literature [8]. The product is a mixture of **III**, **IV** and **V**, one or two of which are major products, and product **V** can only be obtained when reagent **II** is **Il$_{\mathbf{b}}$** (Scheme 3). Compounds **III, IV** and **V** have been separated and characterized, among them, **IV** and **V** are new types of compounds. Compound **III$_{\mathbf{Da}}$** was further characterized by X-ray diffraction analysis.

Scheme 3



a R_3 = H R_4 = Cl
A R_1 = Ph R_2 = Ph(OMe-*p*)
C R_1 = CH_3 R_2 = Ph
E R_1 = Ph R_2 = Ph(Cl-*p*)

b R_3 = Cl R_4 = Cl
B R_1 = CH_3 R_2 = Ph(OMe-*p*)
D R_1 = Ph(OMe-*p*) R_2 = Ph
F R_1 = Ph R_2 = Ph

At room temperature, reaction of chloroacetyl chloride (**II$_{\mathbf{a}}$**) with **I$_{\mathbf{A-F}}$**, followed by the addition of triethyl amine, gave the expected product **III$_{\mathbf{(A-F)a}}$** All of these compounds were in the form of white crystal. The chemical shifts of the three protons on the seven membered ring and the corresponding coupling constants are different. When the 2-position has a methyl group, the NMR signal of proton 4-H is shifted upfield significantly such that it is between the signals of 3-H and 3'-H.

When **I$_{\mathbf{A}}$** and **II$_{\mathbf{b}}$** are reacted at room temperature, product **III$_{\mathbf{Ab}}$** is obtained in 80% yield. However, the product of the reaction between **I$_{\mathbf{B}}$** and **II$_{\mathbf{b}}$**, which is also white crystals, gives an IR spectrum very different from that of **III$_{\mathbf{Ab}}$**. In addition to the typical β-lactam carbonyl absorption at 1700 cm^{-1}, another band at 1640 cm^{-1} is also observed. The mass spectrum shows that four chlorine atoms are present in the molecule. It was therefore concluded that this is a product resulting from one molecule of **I$_{\mathbf{B}}$** reacting with two molecules of **II$_{\mathbf{b}}$**. The NMR spectrum of this compound does not show an AMX signal attributable to the three protons on the seven membered ring, but instead gives a signal corresponding to a 2H doublet with a coupling constant of 7 Hz at δ l.46. Other signals are: δ 3.98 (s, 3H), 4.85 (m, 1H), 4.20 (s, 1 H) and 6.04 (d, 1H, J = 7. 1 Hz). Combining the NMR data with MS fragment analysis, it is reasonable to conclude that the seven membered ring at **I$_{\mathbf{B}}$** fragments during the reaction to give a product with structure **V$_{\mathbf{Bb}}$**. This shows that compounds **II$_{\mathbf{a}}$** and **II$_{\mathbf{b}}$** have different reactivity.

This reaction gives very different results at different temperatures. When carried out at room temperature, **I$_{\mathbf{A}}$** and **Il$_{\mathbf{b}}$** produced **III$_{\mathbf{Ab}}$** as the major product. When carried out at reflux temperature, a compound bearing the structural features of **V$_{\mathbf{Ab}}$** is obtained as the major product. The NMR spectrum of this **V$_{\mathbf{Ab}}$** shows two doublets at δ 6.44 and 6.96 (J = 16 Hz), suggesting that the two protons of the -CH=CH- double bond in **V$_{\mathbf{Ab}}$** are *trans* to each other, while in the case of **V$_{\mathbf{Bb}}$**, these two protons are *ci*s to each other.

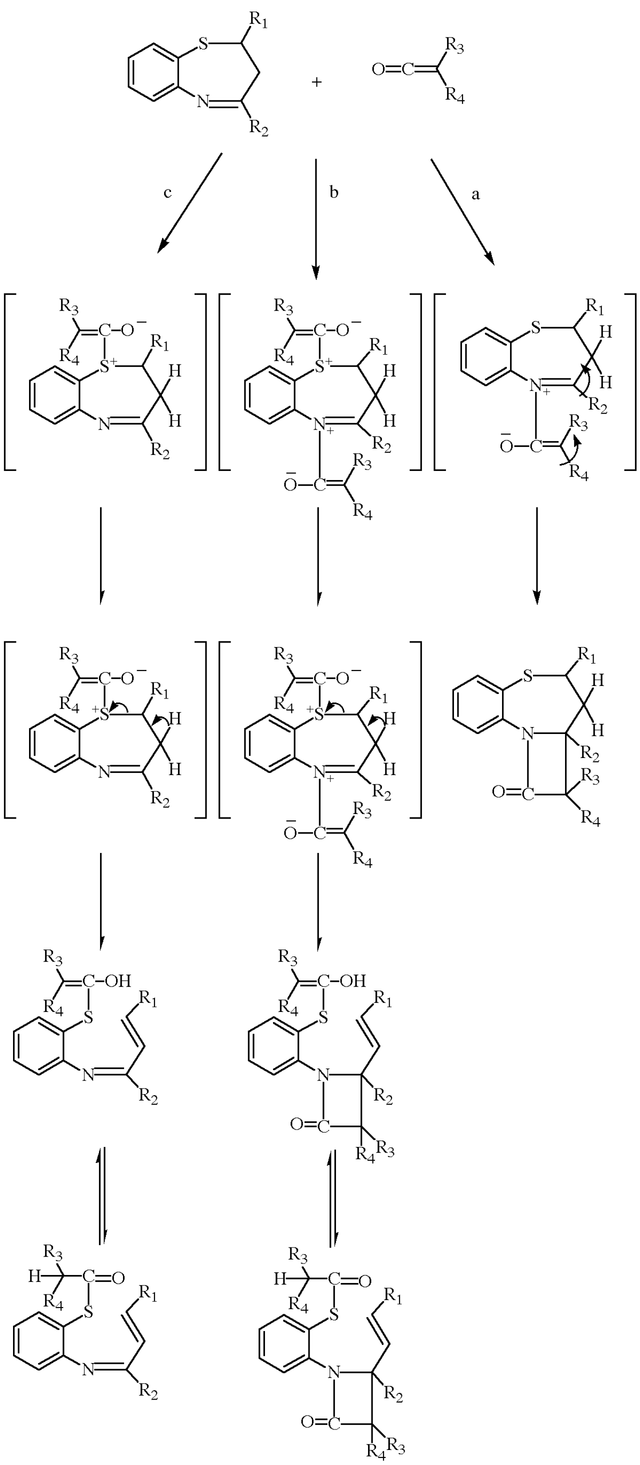
When the reaction of **I$_{\mathbf{A}}$** and **II$_{\mathbf{a}}$** is carried out at reflux temperature, a low melting-point crystalline solid is obtained in addition to a small amount of the expected **III$_{\mathbf{Aa}}$**. The IR spectrum of this compound shows an absorption at 1676 cm^{-1} while the band at 1750 cm^{-1}, which is the typical carbonyl absorption for a β-lactam, is not present. Mass spectrometry shows that this compound has a molecular ion peak with the same m/z value as **III$_{\mathbf{Aa}}$**, but that the fragmentation pattern is different. This suggests that this newly obtained compound is a structural isomer of **III$_{\mathbf{Aa}}$**. The NMR spectrum of this compound did not show signals for the three protons of the AMX system, but showed two doublets at δ 3.50 and 3.95 with a coupling constant of J = 13.5 Hz, and two doublets at δ 6.53 and 6.88 ppm with a coupling constant of J = 15.7 Hz. This indicates that this compound should have the structure of **IV$_{\mathbf{Aa}}$**, with the two protons on the C=C double bond in a *trans* relation.

When **I$_{\mathbf{B}}$** and **II$_{\mathbf{a}}$** are refluxed the low melting-point compound **IV$_{\mathbf{Ba}}$** is obtained along with a small amount of the expected compound **V$_{\mathbf{Ba}}$**. The IR spectrum of **IV$_{\mathbf{Ba}}$** shows an absorption at 1680 cm^{-1}. Its mass spectrom shows an M$^+$ ion with m/z 359, but with a different fragmentation pattern from that of **III$_{\mathbf{Ba}}$**. The NMR spectrum of compound **IV$_{\mathbf{Ba}}$** shows two groups of signals: δ 1.46 (d, 3H, J = 4.8), 3.77 (s, 3H), 4.02 (dd, 2H, J = 13), 4.52 (m, 1H), 5.99 (d, 1H, J = 6.4); 1.48 (d, 3H, J = 4.8), 3.82 (s, 3H), 4.12 (s, 2H), 4.71 (m, 1H), 6.19 (d, 1H, J = 7.1); and 6.85-7.51 (m, 16H) for aromatic protons. The chemical shifts for the major signals of these two compounds are quite similar, with about 0.2 ppm differences. This may indicate that **IV$_{\mathbf{Ba}}$** is a mixture of a pair of stereoisomers.

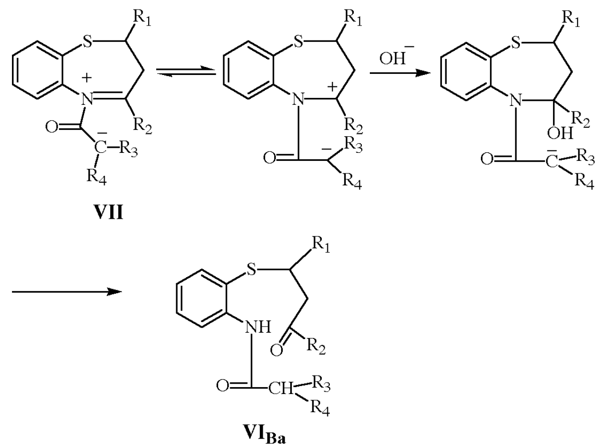
As with the case of **IV$_{\mathbf{Ba}}$**, the NMR spectrum of the reaction product of **I$_{\mathbf{B}}$** with **II$_{\mathbf{b}}$** shows two groups of NMR signals, one of which is described as: δ 1.48 (d, 3H, J = 6.9), 3.80 (s, 3H), 4.54 (m, 1H), 5.99 (d, 1H, J = 7.3), 6.27 (s, 1H); while the other is as follows: δ 1.55 (d, 3H, J = 6.4), 3.82 (s, 3H), 4.79 (m, 1H), 6.24 (s, 1H), 6.27 (d, 1H, J = 7.3). Signals for aromatic protons appear at δ 6.87-7.48 (m, 16H). This suggests that these two compounds may be diastereomers of **IV$_{\mathbf{Ba}}$**. The separation of these diastereomers are in process.

Based on these observations, we can propose the following reaction mechanism (Scheme 4):

Scheme 4



Scheme 5



If the reaction proceeds as proposed, there should be an intermediate **VII**, and a rearrangement should occur with the presence of a nucleophile in the reaction system. When trace amount of water was added to the above reaction system, a different result was obtained. The product with structure **VI** was isolated, indicating the possible existence of intermediate **VII** (Scheme 5):

In conclusion, in the presence of triethylamine, **I** and **II** show different reactivity when bearing different substituents, generating several different products. Additionally, reaction temperature also influences the products obtained. At room temperature, the reaction of **I** and **II** produces **III** as the major product, except that $\mathbf{V_{Bb}}$ is obtained as the major product in the reaction of 2-methyl substrate $\mathbf{I_B}$ with dichloroacetyl chloride. However, when carried out at reflux temperature, as has previously been reported in the literature, the reaction gives very complicated products, which are a mixture of **III**, **IV** and **V** as well as **VI**. Product **V** can be obtained only when reagent **II** is $\mathbf{II_b}$. Compounds **III**, **IV**, **V** and **VI** have all been separated and characterized.

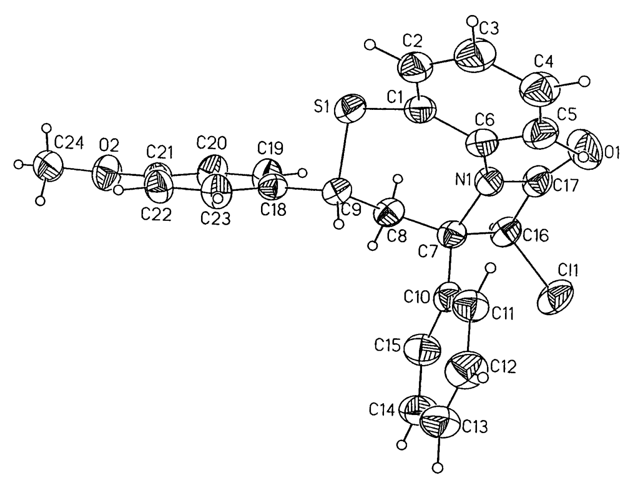


Figure 1. ORTEP drawing of $\mathbf{III_{Da}}$.

EXPERIMENTAL

Melting points were measured on a Yanaco micro melting point apparatus and are uncorrected. Infrared spectra were recorded on Carlzearl Zeiss Jena Specord 75-IR instrument and ^{1}H NMR spectra on a Brucker ARX-400 spectrometer using

Table 1
X-Ray Crystal Structure Determination Summary

Crystal Data	
Empirical Formula	C24 H20 Cl N 02 S
Color; Habit	Colourless and block
Crystal size (mm)	0.40x0.30x0.30
Crystal System	Monoclinic
Space Group	$P2_1/c$
Unit Cell Dimensions	a = 12.547(3)A
b = 10.614(2)A	
c = 15.881(3)A	
b = 105.91(3)°	
Volume	2034.1(10)A^3
Z	4
Formula weight	421.9
Density (calc.)	1.378 Mg/m^3
Absorption Coefficient	0.311 mm^{-1}
F (000)	880
Data Collection	
Diffractometer Used	Rigaku AFC6S
Radiation	MoKa (1 = 0.71073A).
Temperature (K)	293
Monochromator	Highly oriented graphite crystal
2h Range	4.0 to 50.0°
Scan Type	20-w
Scan Speed	Variable, 4.00 to 16.00°/min. in w
Scan Range (w)	1.26°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 0.5% of total scan time
Standard Reflections	3 measured every 150 reflections
Index Ranges	0<h<14, 0<k<12, -18<1<18
Reflections Collected	3137
Independent Reflections	3005 (R_{int}=1.81%)
Observed Reflections	1953 (F> 4.0s (F))
Absorption Correction	Y/A
Solution and Refinement	
System Used	Siemens SHELX-86 (PC Version)
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	Ew $(Fo-Fo)^2$
Absolute Structure	N/A
Extinction Correction	N/A
Hydrogen Atoms	Riding model, fixed isotropic U
Weighting Scheme	$w^{-1} = s^2 (F) + 0.0011F^2$
Number of Parameters Refined	262
Final R Indices (obs. data)	R = 5.10%, wR = 6.47%
R Indices (all data)	R = 10.03%, wR =7.83%
Goodness-of-Fit	1.27
Largest and Mean D/s	0.003, 0.000
Data-to-Parameter Ratio	7.5 : 1
Largest Difference Peak	0.32 eA^{-3}
Largest Difference Hole	0.28 eA^{-3}

Table 2
Atomic Coordinates ($x10^4$) and Equivalent Isotropic Displacement Coefficients (A^2x10^3)

x	y	z	U (eq)	
Cl(1)	3297(1)	7481(1)	8878(1)	62(1)
S(1)	1269(1)	2162(1)	7767(1)	44(1)
O(1)	2356(3)	5472(3)	10141(2)	65(2)
O(2)	-1393(3)	2377(3)	3744(2)	53(1)
N(1)	2632(3)	4346(3)	8952(2)	36(1)
C(1)	2354(4)	2060(4)	8746(3)	37(2)
C(2)	2617(4)	857(4)	9084(3)	43(2)
C(3)	3342(4)	672(5)	9901(3)	51(2)
C(4)	3845(4)	1585(5)	10388(3)	52(2)
C(5)	3618(4)	2885(4)	10053(3)	47(2)
C(6)	2880(4)	3083(4)	9240(3)	37(2)
C(7)	2591(4)	5057(4)	8127(3)	36(2)
C(8)	1611(4)	4693(4)	7368(3)	39(2)
C(9)	1649(4)	3342(4)	7051(3)	36(2)
C(10)	3680(4)	5108(4)	7889(3)	37(2)
C(11)	4611(4)	4451(5)	8339(3)	49(2)
C(12)	5596(4)	4539(5)	8106(4)	60(2)
C(13)	5662(5)	5304(5)	7437(4)	61(2)
C(14)	4750(5)	5981(5)	6978(4)	58(2)
C(15)	3763(4)	5883(4)	7198(3)	51(2)
C(16)	2328(4)	6233(4)	8637(3)	41(2)
C(17)	2428(4)	5371(4)	9407(3)	44(2)
C(18)	837(3)	3095(4)	6163(3)	37(2)
C(19)	-130(4)	3779(5)	5850(3)	51(2)
C(20)	-850(4)	3503(5)	5049(3)	50(2)
C(21)	-641(4)	2540(4)	4536(3)	39(2)
C(22)	318(4)	1850(5)	4847(3)	44(2)
C(23)	1031(4)	2122(4)	5644(3)	44(2)
C(24)	-1316(4)	1271(5)	3268(3)	55(2)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 3
Bond lengths (A)

Cl(1)-C(16)	1.768(5)	S(1)-C(1)	1.766(4)
S(1)-C(9)	1.840(5)	O(1)-C(17)	1.199(7)
O(2)-C(21)	1.361(5)	N(1)-C(6)	1.423(5)
N(1)-C(7)	1.500(6)	N(1)-C(17)	1.368(6)
C(1)-C(2)	1.389(6)	C(1)-C(6)	1.396(6)
C(2)-C(3)	1.380(6)	C(3)-C(4)	1.374(7)
C(5)-C(6)	1.383(6)	C(7)-C(8)	1.517(6)
C(7)-C(10)	1.515(7)	C(7)-C(16)	1.571(6)
C(8)-C(9)	1.525(6)	C(9)-C(18)	1.519(5)
C(10)-C(11)	1.379(6)	C(10)-C(15)	1.398(7)
C(11)-C(12)	1.387(8)	C(12)-C(13)	1.358(9)
C(13)-C(14)	1.378(8)	C(14)-C(15)	1.379(9)
C(16)-C(17)	1.504(7)	C(18)-C(19)	1.384(6)
C(19)-C(20)	1.376(6)	C(20)-C(21)	1.376(7)
C(21)-C(22)	1.379(6)	C(22)-C(23)	1.366(6)

$CDCl_3$ as solvent and Me_4Si as internal standard. Mass spectra were obtained from 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.

General Procedure for the Synthesis of Substituted-2,2a,3,4-tetrahydro-1*H*-azeto[2,1-*d*][1,5]benzothiazepine (**III**).

To a mixture of 1.5 mmol of compound **I**, 40 ml of anhydrous benzene and 3 mmol of chloroacetyl chloride (**II$_a$**) was added a

Table 4
Bond angles (°)

C(1)-S(1)-C(9)	108.6(2)	C(21)-O(2)-C(24)	117.9(4)
C(6)-N(1)-C(7)	135.0(4)	C(7)-N(1)-C(17)	95.4(3)
S(1)-C(1)-C(2)	116.1(3)	S(1)-C(1)-C(6)	125.4(3)
C(2)-C(1)-C(6)	118.2(4)	C(1)-C(2)-C(3)	121.3(4)
C(3)-C(4)-C(5)	119.5(4)	C(4)-C(5)-C(6)	121.0(4)
N(1)-C(6)-C(1)	121.6(4)	N(1)-C(6)-C(5)	118.4(4)
C(1)-C(6)-C(5)	120.0(4)	N(1)-C(7)-C(8)	113.0(4)
N(1)-C(7)-C(10)	114.7(3)	C(8)-C(7)-C(10)	113.7(4)
N(1)-C(7)-C(16)	84.9(3)	C(8)-C(7)-C(16)	111.9(4)
C(10)-C(7)-C(15)	115.6(4)	C(7)-C(8)-C(9)	114.2(3)
S(1)-C(9)-C(8)	113.5(3)	S(1)-C(9)-C(18)	103.6(3)
C(8)-C(9)-C(18)	113.3(3)	C(7)-C(10)-C(11)	123.1(4)
C(7)-C(10)-C(15)	118.9(4)	C(11)-C(10)-C(15)	118.0(5)
C(11)-C(12)-C(13)	119.9(5)	C(12)-C(13)-C(14)	120.4(6)
C(13)-C(14)-C(15)	120.0(5)	C(10)-C(15)-C(14)	120.5(5)
Cl (1)-C(16)-C(7)	118.5(4)	Cl (1)-C(16)-C(17)	112.3(3)
C(7)-C(16)-C(17)	87.3(3)	O(1)-C(17)-N(1)	131.3(5)
O(1)-C(17)-C(16)	136.4(5)	N(1)-C(17)-C(16)	92.3(4)
C(9)-C(18)-C(23)	119.9(4)	C(19)-C(18)-C(23)	117.2(4)
C(18)-C(19)-C(20)	120.6(5)	C(19)-C(20)-C(21)	121.5(4)
O(2)-C(21)-C(20)	116.4(4)	O(2)-C(21)-C(22)	125.3(4)
C(20)-C(21)-C(22)	118.2(4)	C(21)-C(22)-C(23)	120.3(5)
C(18)-C(23)-C(22)	122.1(4)		

Table 5
Anisotropic Displacement Coefficients (A^2x10^3)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl(1)	65(1)	36(1)	85(1)	-15(1)	22(1)	-17(1)
S(1)	48(1)	37(1)	46(1)	-10(1)	11(1)	0(1)
O(1)	91(3)	56(2)	57(3)	5(2)	34(2)	-12(2)
O(2)	55(2)	51(2)	43(2)	1(2)	-1(2)	-2(2)
N(1)	41(2)	30(2)	37(2)	1(2)	11(2)	0(2)
C(1)	37(3)	36(3)	42(3)	-4(2)	16(2)	0(2)
C(2)	50(3)	36(3)	47(3)	-4(2)	17(3)	2(2)
C(3)	54(3)	39(3)	59(4)	-1(3)	15(3)	10(3)
C(4)	50(3)	49(3)	53(3)	-3(3)	8(3)	13(3)
C(5)	50(3)	39(3)	51(3)	-8(2)	13(3)	4(2)
C(6)	36(3)	33(3)	46(3)	-2(2)	17(2)	0(2)
C(7)	43(3)	24(2)	43(3)	-1(2)	14(2)	-1(2)
C(8)	41(3)	28(2)	45(3)	2(2)	8(2)	5(2)
C(9)	34(3)	32(2)	42(3)--	3(2)	10(2)	0(2)
C(10)	42(3)	28(2)	42(3)	-4(2)	11(2)	-6(2)
C(11)	42(3)	53(3)	53(3)	0(3)	17(3)	2(3)
C(12)	39(3)	68(4)	74(4)	6(3)	18(3)	-2(3)
C(13)	54(4)	69(4)	68(4)	-8(3)	31(3)	-5(3)
C(14)	65(4)	52(3)	67(4)	-10(3)	32(3)	2(3)
C(15)	52(3)	46(3)	58(3)	3(3)	20(3)	6(3)
C(16)	40(3)	27(2)	54(3)	2(2)	12(2)	-5(2)
C(17)	42(3)	40(3)	51(3)	-3(2)	17(3)	-14(3)
C(18)	31(3)	40(3)	40(3)	-2(2)	10(2)	2(2)
C(19)	42(3)	52(3)	58(4)	9(3)	11(3)	-14(3)
C(20)	37(3)	51(3)	56(3)	6(2)	1(3)	-5(3)
C(21)	39(3)	42(3)	34(3)	-3(2)	6(2)	1(2)
C(22)	43(3)	48(3)	42(3)	5(2)	12(2)	-7(2)
C(23)	43(3)	42(3)	48(3)	10(2)	12(2)	-3(2)
C(24)	49(3)	70(4)	47(3)	-13(3)	15(3)	-10(3)

The anisotropic displacement exponent takes the form:
$-2p^2 (h^2a^{*2}U11 +.... + 2hka^*b^*U12)$

Table 6
H-Atom Coordinates (x 10^4) and Isotropic Displacement Coefficients (A^2x10^3)

	x	y	z	U
H(2)	2287	141	8742:	80
H(3)	3495	-167	10130	80
H(4)	4351	1560	10956	80
H(5)	3977	3594	10390	80
H(8A)	947	4794	7551	80
H(8B)	1590	5250	6888	80
H(9)	2406	3260	7038	80
H(11)	4576	3924	8822	80
H(12)	6230	4059	8418	80
H(13)	6347	5373	7282	80
H(14)	4801	6521	6506	80
H(15)	3128	6351	6874	80
H(16)	1687	6735	8372	80
H(19)	-301	4452	6196	80
H(20)	-1514	3993	4842	80
H(22)	484	1175	4501	80
H(23)	1689	1622	5850	80
H(24A)	-1891	1273	2725	80
H(24B)	-1399	546	3605	80
H(24C)	-606	1243	3149	80

solution of 3 mmol triethylamine in 40 ml benzene over a period of 2 hours. The triethylamine hydrochloric acid salt was removed by filtration after completing the addition. The filtrate was washed with 5% sodium bicarbonate, then with brine, and dried over anhydrous sodium sulfate. The solution was concentrated and the residue was separated through silica gel chromatography using cyclohexane/ethyl acetate = 5:3 as the eluant. The isolated solid was recrystallized in ethanol. The product can also be isolated through crystallization of the crude product from ethanol.

2-Chloro-2,2a,3,4-tetrahydro-2a-(4-methoxyphenyl)-4-phenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one (**III_{Aa}**).

Compound **III_{Aa}** was obtained as white crystal, yield 51%, melting point: 178-9 °C; IR (cm^{-1}): 1740, 1610. MS: M^+, 421, 386, 282, 241 (100), 226, 133. ^1H NMR (CD_3Cl): δ 3.15 (dd, 1H, J = 14, 11), 3.62 (d, 1H, J = 14), 3.83 (s, 1H), 4.03 (d, 1H, J = 11.0), 5.08 (s, 1H), 6.92-7.96 (m, 13H).

Anal. Calcd. for $C_{24}H_{20}NO_2SCl$: C, 68.41, H, 4.75, N, 3.33; found: C, 68.49, H, 4.67, N, 3.26.

2-Chloro-2,2a,3,4-tetrahydro-2a-(4-methoxyphenyl)-4-methyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one (**III_{Ba}**).

Compound **III_{Ba}** was obtained as white crystal, yield 69%, melting point: 162-3 °C; IR (cm^{-1}): 1750, 1600. MS: M^+, 359, 324, 283, 241(100), 138, 113. ^1H NMR (CD_3Cl): δ 1.41 (d, 3H, J = 7.2), 2.53 (q, 1H, J = 14, 11), 2.96 (m, 1H), 3.26 (dd, 1H, J = 14, 0), 4.96 (s, 1H), 6.85-7.88 (m, 9H).

Anal. Calcd. for $C_{19}H_{18}NO_2SCl$: C, 63.51, H, 5.01, N, 3.90; found: C, 63.70, H, 4.96, N, 3.85.

2-Chloro-2,2a,3,4-tetrahydro-2a-phenyl-4-methyl-1*H*-azeto-[2,1-*d*][1,5]benzothiazepin-1-one (**III_{Ca}**).

Compound **III_{Ca}** was obtained as white crystal, yield 64%, melting point: 161-2 °C; IR (cm^{-1}): 1768, 1571. MS: M^+, 329, 294, 253, 211, 136, 77. ^1H NMR(CD_3Cl): δ 1.37, (d, 3H, J = 7.2), 2.54 (q, 1H, J = 14, 11), 2.96 (m, 1H), 3.29 (dd, 1H, J = 14, 1), 4.96 (s, 1H), 7.13-7.91 (m, 9H).

Anal. Calcd for $C_{18}H_{16}NOSCl$: C, 65.65, H, 4.86, N, 4.25; found: C, 65.65, H, 4.84, N, 3.98.

2-Chloro-2,2a,3,4-tetrahydro-2a-phenyl-4-(4-methoxyphenyl)-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one (**III$_{Da}$**).

Compound **IIIDa** was obtained as white crystal, yield 47%, melting point: 196-8 °C; IR (cm^{-1}): 1778, 1607. MS: M$^+$, 421, 386, 270, 235, 211, 134. ^{1}H NMR (CD_3Cl): δ 3.10 (dd, 1H, J = 14, 11), 3.60 (d, 1H, J = 14, 0), 3.82 (s, 3H), 3.93 (d, 1H, J = 11.0), 5.05 (s, 1H), 6.89-7.96 (m, 13H).

Anal. Calcd. for $C_{24}H_{20}NO_2SCl$: C, 68.41, H, 4.75, N, 3.33; found: C, 68.42, H, 4.74, N, 3.07.

2-Chloro-2,2a,3,4-tetrahydro-2a-(4-chlorophenyl)-4-phenyl-1*H*-azeto[2,l-*d*][1,5]benzothiazepin-1-one (**III$_{Ea}$**).

Compound **III$_{Ea}$** was obtained as white crystal, yield 80%, melting point: 207-8 °C; IR (cm^{-1}): 1780, 1596. MS: M$^+$, 425, 286, 245(100), 204, 108, 77. ^{1}H NMR (CD_3Cl): δ 3.14 (dd, 1H, J = 14, 11), 3.56 (dd, 1H, J = 14, 1), 3.91 (d, 1H, J = 11), 5.06 (s, 1H), 7.20-7.95 (m, 13H).

Anal. Calcd. for $C_{23}H_{17}NOSCl_2$: C, 64.94, H, 4.00, N, 3.29; found: C, 64.71, H, 4.01, N, 3.18.

2-Chloro-2,2a,3,4-tetrahydro-2a-phenyl-4-phenyl-1*H*-azeto-[2,1-*d*][1,5]benzothiazepin-1-one (**III$_{Fa}$**).

Compound **III$_{Fa}$** was obtained as white crystal, yield 50%, melting point: 198-9 °C; ^{1}H NMR (CD_3CI): δ 3.16 (dd, 1H, J = 14, 11), 3.61 (dd, 1H, J = 14, 1), 3.92 (d, 1H, J = 11), 5.05 (s, 1H), 7.15-7.97 (m, 14H).

Anal. Calcd for $C_{23}H_{18}NOSCl$: C, 70.59, H, 4.60, N, 3.58; found: C, 71.31, H, 4.58, N, 3.52.

2,2-Dichloro-2,2a,3,4-tetrahydro-2a-(4-methoxyphenyl)-4-phenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one (**III$_{Ab}$**).

Compound **III$_{Ab}$** was obtained as white crystal, yield 83%, melting point: 184-5 °C; IR (cm^{-1}): 1760, 1620. MS: M$^+$, 455, 420, 385, 241, 77. ^{1}H NMR (CD_3Cl): δ 3.43 (d, 1H), 3.44 (s, 1H), 3.79 (s, 3H), 3.93 (t, 1H), 6.81-7.91 (m, 13H).

Anal. Calcd for $C_{24}H_{19}NO_2SCl_2$: C, 63.30, H, 4.18, N, 3.07; found: C, 63.05, H, 4.20, N, 3.08.

General Procedure for the Synthesis of Substituted Imine(**IV**).

To a mixture containing 3 mmol of **I** and 6 mmol of chloroacetyl chloride (**Ila**) in 60 ml of anhydrous benzene was added a solution of 6 mmol of triethylamine in 60 ml of anhydrous benzene over a period of 2 hours under reflux. The triethylamine hydrochloric acid salt thus formed was removed by filtration and the filtrate was washed with 5% aqueous sodium bicarbonate followed by brine. The organic layer was dried over anhydrous sodium sulfate, concentrated and the residue was separated through silica gel using cyclohexane/ethyl acetate = 5:3 as the eluant. The separated fractions were concentrated and the solid was recrystallized from ethanol.

2-Chloro-l-{[2-[4-methoxy-α-(2-phenylethenyl)-benzylideneamino]-phenyl]thio)ethanone (**IV$_{Aa}$**).

Compound **IV$_{Aa}$** was obtained as pale-yellowish crystals, yield 34%, melting point: 54-5 °C; IR (cm^{-1}): 1676, 1605. MS: M$^+$, 421, 386, 344, 241(100), 151, 77. ^{1}H NMR (CD_3CI): δ 3.50 (d, 1H, J = 13.5), 3.83 (s, 3H), 3.95 (d, 1H, J = 13.5), 6.53 (d, 1H, J = 15.7), 6.88 (d, 1H, J = 15.7), 6.91-7.66 (m, 13H).

Anal. Calcd for $C_{24}H_{20}NO_2SCl$: C, 68.41, H, 4.75, N, 3.33; found: C, 68.41, H, 4.81, N, 3.12.

2-Chloro-l-{[2-[4-methoxy-α-(2-propenyl)-benzylideneamino]-phenyl]thio}ethanone (**IV$_{Ba}$**).

Compound **IV$_{Ba}$** was obtained as pale-yellowish crystals, yield 23%, melting point: 150-1 °C; IR (cm^{-1}): 1684, 1605. MS: M$^+$, 359, 310, 282(100), 242, 134, 77. ^{1}H NMR (CD_3Cl): δ 1.46 (d, 3H, J = 4.8), 3.77 (s, 3H), 4.02 (dd, 2H, J = 13), 4.52 (m, 1H), 5.99 (d, 1H, J = 6.4), δ 1.48 (d, 3H, J = 4.8), 3.82 (s, 3H), 4.12 (s, 2H), 4.71 (m, 1H), 6.19 (d, 1H, J = 7.1). 6.85-7.51 (m, 16H).

Anal. Calcd for $C_{19}H_{18}NOSCl$: C, 63.51, H, 5.01, N, 3.90; found: C, 63.73, H, 4.92, N, 3.75.

2,2-Dichloro-1-{[2-[4-methoxy-α-(2-propenyl)-benzylideneamino]-phenyl]thio}ethanone (**IV$_{Bb}$**).

Compound **IV$_{Bb}$** was obtained as white crystal, yield 53%, melting point: 174-5 °C; IR (cm^{-1}): 1680, 1600. MS: M$^+$, 393, 358, 310(100), 282, 242, 159. ^{1}H NMR (CD_3Cl): δ 1.48 (d, 3H, J = 6.9), 3.80 (s, 3H), 4.54 (m, 1H), 5.99 (d, 1H, J = 7.3), 6.27 (d, 1H, J = 7.3); δ 1.55 (d, 3H, J = 6.4), 3.82 (s, 3H), 4.79 (m, 1H), 6.24 (s, 1H), 6.27 (d, 1H, J = 7.3); 6.87-7.48 (m, 16H).

Anal. Calcd for $C_{19}H_{17}NO_2SCl_2$: C, 58.02, H, 4.33, N, 3.56; found: C, 57.60, H, 4.48, N, 3.34.

General Procedures for the Synthesis of Substituted β-Lactam **V$_{Ab}$**.

To a mixture of 3 mmol of **I** and 6 mmol of dichloroacetyl chloride (**II$_b$**) in 60 ml of anhydrous benzene was added a solution of 6 mmol triethylamine in 60 ml of anhydrous benzene over a period of 2 hours under reflux. The reaction mixture was filtered and concentrated to give a brownish viscous liquid. Crystallization of the liquid gave the products.

3,3-Dichloro-l-[2-(2,2-dichloro-l-oxoethylthio)phenyl]-4-(4-methoxyphenyl)-4-(l-phenylvinyl)-2-azetidinone (**V$_{Ab}$**).

Compound **V$_{Ab}$** was obtained as white crystal, yield 57%, melting point: 216-8 °C; IR(cm^{-1}): 1790, 1690, 1584. MS: 566(M+1), 532, 456, 420, 346, 242, 91(100). ^{1}H NMR (CD_3Cl): δ 3.82 (s, 3H), 6.06 (s, 1H), 6.44 (d, 1H, J = 16), 6.96 (d, 1H, J = 16), 6.88-7.62 (m, 13H).

Anal. Calcd for $C_{26}H_{19}NO_3SCl_4$: C, 55.22, H, 3.36, N, 2.48; found: C, 54.91, H, 3.51, N, 2.31.

3,3-Dichloro-1-[2-(2,2-dichloro-1-oxoethylthio)phenyl]-4-(4-methoxyphenyl)-4-(1-propenyl)-2-azetidinone (**V$_{Bb}$**).

Compound **V$_{Bb}$** was obtained as white crystal, yield 70%, melting point: 130-1 °C; IR(cm^{-1}): 1770, 1640, 1600. MS: 505(M+2), 469, 317, 235, 198, 43(100). ^{1}H NMR (CD_3Cl): δ 1.46 (d, 3H, J = 7.0), 3.79 (s, 3H), 4.85 (m, 1H), 4.20 (s, 1H), 6.04 (d, 1H, J = 7.1), 6.82-7.35 (m, 8H).

Anal. Calcd for $C_{21}H_{17}NO_3SC1_4$: C, 50.10, H, 3.38, N, 2.78; found: C, 49.86, H, 3.50, N, 2.88.

Procedure for the Synthesis of 4-[2-(2-Chloro-1-oxoethylamino)phenyl]thio-l-(4-methoxyphenyl)-2-petanone (**VI$_{Ba}$**).

To a mixture of 3 mmol of **I** and 6 mmol of chloroacetyl chloride (**Ilb**) in 60 ml of anhydrous benzene was added a solution of 6 mmol of triethylamine (triethylamine was used without drying treatment) in 60 ml of anhydrous benzene over a period of 2 hours under reflux. The reaction mixture was filtered and concentrated to give a brownish viscous liquid. Crystallization of the liquid gave product as pale-brownish crystals, yield 21%, melting point: 102-3 °C; IR(cm^{-1}): 1668, 1598. MS: M^+, 377, 177, 135(100), 124, 107, 92, 77.

Anal. Calcd for $C_{19}H_{20}NO_3SCl$: C, 60.48, H, 5.31, N, 3.71; found: C, 60.29, H, 5.17, N, 3.32.

Acknowledgements.

This work was supported by the National Natural Scientific Foundation of China (No. 29972001) and the ASP Fund of the Hong Kong Polytechnic University.

REFERENCES AND NOTES

[1a] A. Levai. *Heterocycl. Commun.,* **3**, 211 (1997); [b] H. Inoue, M. Konda, T. Hashiyama, H. Otsuka, A. Watanabe, M. Gaino, K. Takahashi, T. Date, K. Okamura, M. Takeda, H. Narita, S. Murata, A. Odawara, H. Sasaki and T. Nagao. *Chem. Pharm. Bull.* **45**, 1008 (1997); [c] K. Seio, H. Tanaka, T. Kohara, K. Hashimoto, M. Fujimura, H. Horiuchi, H. Yasumatsu and K. Kimura. PCT Int. Appl. WO 99 11,647 (1999); *Chem. Abstr.,* **130**, 223304 (1999); [d] I. Tsujioka, H. Matsumae, T. Nishida and T. Shibatani. PCT Int. Appl. WO 99 07,875 (1999); *Chem. Abstr.,* **130**, 167246 (1999); [e] T. Patonay, W. Adam, J. Jeko, K. E. Kover, A. Levai, M. Nemeth and K. Peters. *Heterocycles,* **51**, 85 (1999); [f] A. Chimirri, R. Gitto, S. Grasso, A. M. Monforte and M. Zappala, *Advances in Heterocyclic Chemistry,* **63**, 61 (1995).

[2] G. Grandolini, L. Perioli, V. Ambrogi, *Eur. J. Med. Chem.,* **34**, 701 (1999).

[3] A. Levai, *Pharmazie* **54**, 719 (1999).

[4] V. Darias, C. C. Sanchez-Mateo, M. A. Exposito-Orta, L. M. Albertos, J. A. Diaz and S. Vega., *Pharmazie,* **54**, 783 (1999).

[5] V. R. Naik, H. B. Naik, *Asian J. Chem.* **11**, 661 (1999).

[6a] E. Manghisi, B. Perego, WO 92 10485 (1992); *Chem. Abstr.,* **118**, 38961 (1993); [b] F. L. Piselli, P. Boschi, C. Navoni, EP 594101 (1994); *Chem. Abstr.,* **121**, 9433 (1995).

[7] For examples: [a] John D. Buynak and B. Bachmann. PCT Int. Appl. WO 96 17848 (1996); *Chem. Abstr.,* **125**, 114392 (1997). [b] G. Cainelli, P. Galletti, D. Giacomini. *Synlett.* **611** (1998) [c] H. Arai, Y. Matsushima, T. Eguchi, K. Shindo and K. Kakihuma *Tetrahedron Lett.* **39**, 3181(1998); [d] S. A. Avetisyan, S. L. Kocharov, L. V. Azaryan, I. A. Dzhagatspanyan and G. G. Melikyan, *Khim. Farm. Zh.* **32**, 3 (1998).

[8a] C. Wang, PhD. dissertation, Peking University, (1988); [b] A. Szollosy and G. Kotorych, *Can. J. Chem.,* **66**, 279 (1988).

[9a] R. X. Lan and S. Jin, *Chinese Chem. Lett.,* **3**, 179 (1992); [b] X. Y. Zhang and S. Jin, *Chinese Chem. Lett.,* **3**, 181 (1992); [c] J. X. Xu, H. T. Wu and S. Jin, *Chinese J. Chem.,* **17**, 84 (1999).

[10] J. X. Xu, R. X. Lan and S. Jin, *Chem. J. Chinese Univ.,* **19**, 1774 (1998).

[11] B. Y. Mi and S. Jin, *Chinese Chem. Lett.,* **2**, 925 (1991).

[12] D. Yao, B. Y. Mi, S. Jin and X. L. Jin, *Hecheng Huaxue,* **6**, 272 (1998).

[13] H. Z. Wang, D. Yao, R. X. Lan, J. X. Xu and S. Jin, *Chinese Chem. Lett.,* **10**, 625 (1999).