SYNTHESIS OF β-LACTAM DERIVATIVES OF 1,5-BENZOXAZEPINES AND 1,5-BENZOTHIAZEPINES

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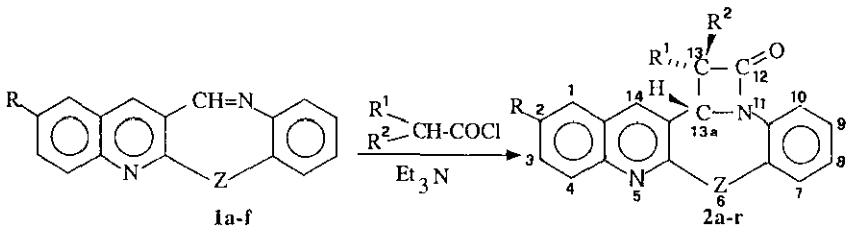
Abstract - Condensed β-lactam derivatives of 1,5-benzoxazepines (**2a-i**) and of 1,5-benzothiazepines (**2j-r**) have been synthesized by the reaction of quino[2,3-b][1,5]benzoxazepines (**1a-c**) or the corresponding benzothiazepines (**1d-f**) with some acyl chlorides in the presence of triethylamine. The formyl chloroacetamido derivatives (**4a,b**) were instead obtained by treating **1a,d** with chloroacetyl chloride in the absence of the base. The mechanism of the reactions is discussed. No antibacterial activity was shown by the title compounds (**2a-r**) in the test experimental conditions.

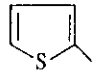
Condensed β-lactam derivatives of 1,5-benzothiazepines have been recently prepared by the well known cycloaddition reaction of imines with the acyl chloride/Et_3N system.[1] In earlier papers we have described the synthesis of the tetracyclic quino[2,3-b][1,5] benzoxazepines[2] and of the corresponding benzothiazepines.[3]
We report here on the cycloaddition of the above "fixed" [4] imines (**1a-f**) with several acyl chlorides.Treatment of benzoxazepines (**1a-c**) or benzothiazepines (**1d-f**) with the appropriate acyl chloride in the presence of Et_3N in refluxing benzene for 1 h, following the procedure of Szöllösy et al., [1] afforded the β-lactams (**2a-r**) as the only isolable products (Scheme 1).



1a-f **2a-r**

a: Z=O; R=H
b: Z=O; R=Me
c: Z=O; R=Cl
d: Z=S; R=H
e: Z=S; R=Me
f: Z=S; R=Cl

a: Z=O; R=H; R^1=H; R^2=Cl
b: Z=O; R=H; R^1=H; R^2=T
c: Z=O; R=H; R^1=Cl; R^2=Cl
d: Z=O; R=Me; R^1=H; R^2=Cl
e: Z=O; R=Me; R^1=H; R^2=T
f: Z=O; R=Me; R^1=Cl; R^2=Cl
g: Z=O; R=Cl; R^1=H; R^2=Cl
h: Z=O; R=Cl; R^1=H; R^2=T
i: Z=O; R=Cl; R^1=Cl; R^2=Cl
j: Z=S; R=H; R^1=H; R^2=Cl
k: Z=S; R=H; R^1=H; R^2=T
l: Z=S; R=H; R^1=Cl; R^2=Cl
m: Z=S; R=Me; R^1=H; R^2=Cl
n: Z=S; R=Me; R^1=H; R^2=T
o: Z=S; R=Me; R^1=Cl; R^2=Cl
p: Z=S; R=Cl; R^1=H; R^2=Cl
q: Z=S; R=Cl; R^1=H; R^2=T
r: Z=S; R=Cl; R^1=Cl; R^2=Cl

T = 

Scheme 1. One of the enantiomers only shown

Table 1. Yields [a] and melting points of 13,13a-dihydro-12H-azeto[2,1-d]quino[2,3-b]-[1,5]benzoxazepin-12-ones (**2a-i**) and corresponding benzothiazepin-12-ones (**2j-r**).

Compound	Yield %	mp, °C	Crystallization solvent [b]
2a	97	187.5-188.5	EA
2b	93	124-132	EA-H
2c	92	178-179	EA
2d	83	171-172	EA-H
2e	90	122-122.5	D-H
2f	91	193-194	EA
2g	92	196.5-197	EA
2h	89	126-127	EA-H
2i	93	220-222	EA
2j	91	257-260	D
2k	93	159-161	EA-H
2l	91	271-271.5	D-EA
2m	98	208-209	EA
2n	95	118-119	EA-H
2o	89	185-185.5	EA
2p	77	264-266	D-H
2q	90	206-207	D-H
2r	91	192-193	EA-LP

[a] Yields from weights of homogeneous chromatographic fractions.
[b] D = dichloromethane; EA = ethyl acetate; H = n-hexane; LP = light petroleum (40-60 °C bp fraction).

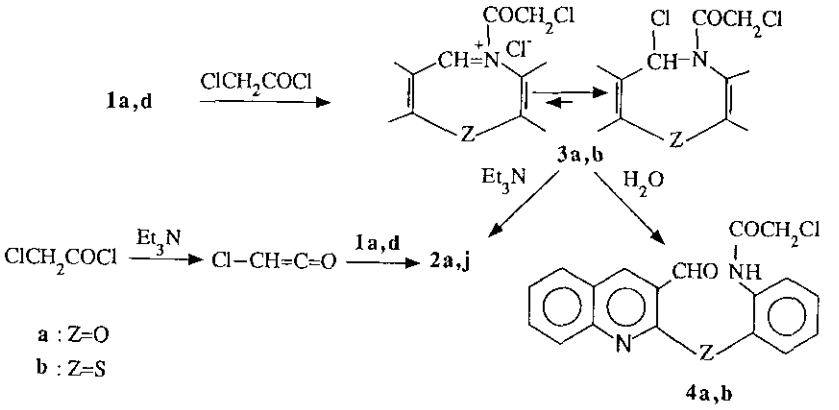
The structure of these new compounds is supported by analytical data and spectroscopic evidence. The most diagnostic feature in the ^{1}H nmr spectra of the pentacyclic derivatives (**2a-r**) is the resonance of the β-lactam protons. The relative configuration of these protons, in derivatives obtained by the reaction of a prochiral acyl chloride (R^1= H, R^2= Cl or T) with the achiral imine (**1**), can be inferred by the magnitude of their vicinal coupling.[5] On the basis of the low $J_{13\text{-}13a}$ values (2.4 or 2.8 Hz in products containing R^2= Cl or T respectively), the trans stereochemistry has to be assigned to the β-lactam ring of both oxazepine (**2a,b,d,e,g,h**) and thiazepine (**2j,k,m,n,p,q**) derivatives. The correpondindig cis diastereomers could never be detected. It is noteworthy that, while the 13-H signal ever occurs as a sharp doublet in the spectra of the above compounds, the 13a-H resonance appears as a doublet in the spectra of benzothiazepine derivatives (**2j,k,m,n,p,q**) and as an unresolved doublet or multiplet in those of benzoxazepine derivatives (**2a,b,d,e,g,h**). A long range coupling between the 13a-H and an aromatic proton, favoured by the conformation adopted by the condensed benzoxazepine system, could account for the observed ^{1}H nmr pattern.

In our experimental conditions (Et_3N is added first to the solution of the imine) the preliminary formation of the ketene, by dehydrochlorination from the acyl chloride, should be the key step in the synthesis of the β-lactams (**2**).[6] On the other hand, the direct formation of β-lactams from imines and acyl chlorides in the absence of Et_3N has been previously reported.[6,7] In these cases the reaction of the acyl chloride with the imine produces an adduct, which cyclizes after an intramolecular deprotonation. Duran and Ghosez[8] isolated an 1:1 adduct by the reaction at room temperature of dichloroacetyl chloride with benzalaniline in the absence of Et_3N. This intermediate then formed the corresponding β-lactam on melting or refluxing in benzene solution.

In order to get further informations on the mechanistic aspects of the here reported cycloaddition reaction, we refluxed a benzene solution of benzoxazepine (**1a**) with chloroacetyl chloride in the absence of the base for 1 h. The same experiment was then carried out on the benzothiazepine (**1d**). In both cases we isolated the formyl chloroacetamido derivatives (**4a,b**), probably arising from the hydrolysis of the intermediate adducts (**3a,b**) (Scheme 2) during the final partition between ethyl acetate and water, and the corresponding β-lactams (**2a** and **2j**) could not be detected. Recently Veerabhadraiah et al.[9] have described the formation of chloroacetamido derivatives, instead of the expected β-lactams, by the reaction of Schiff's bases (2-benzalaminothiazolylcoumarins) with chloroacetyl chloride in the presence of Et_3N in dioxane.

Finally **1a** or **1d** was refluxed in benzene with chloroacetyl choride for 1 h and then Et_3N was added. After refluxing for 1 h, the β-lactams (**2a** and **2j**) were isolated in poor yield (38% in both cases) by usual work up and chromatographic separation.

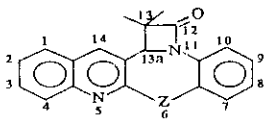
From all our reported results it follows that, unlike the above mentioned cases,[6,7] the Et_3N plays an essential role in the cycloaddition reaction,which leads to **2a-r.** Furthermore the ketene pathway appears to be favoured over the acylation of the imine by the acyl chloride.
In order to gain evidence for the structure of the intermediate adducts (**3a,b**), the reaction of **1a** or **1d** with chloroacetyl chloride was performed in refluxing deuteriobenzene and the ^1H nmr spectra of the final solutions were runned on before the conventional work up, which leads to the above described derivatives (**4a,b**). The upfield shift of the resonance of the iminic proton of **1a** and **1d** ($\Delta\ \delta$=0.44 and 0.76 respectively), after the treatment with the acyl chloride, allows to assign the covalent rather than N-acyliminium structure [10] to the intermediate (**3a,b**).



Scheme 2

The antibacterial activity of the β-lactam drugs was tested by diffusion method[11] in solid medium using both Gram-positive (S. aureus ATCC 25923) and Gram-negative (E. Coli ATCC 25922) strains.
Tests were carried out in 20 µl of dimethyl sulphoxide solutions containing 100 - 10 - 1 µg of the tested drugs by sterile paper disks (Ø 6 mm) on Mueller-Hinton Agar plates inoculated with 10^5 CFU (Colonies Forming Units). The plates were incubated for 18 h at 37 °C. Tests were performed in comparison to Ampicillin and Cephaloridine at the same concentration. The screening results of the tested drugs showed no antibacterial activity in the applied experimental conditions.

Table 2. Selected spectral data and microanalysis for 2a-r



Compound	^{1}H nmr (δ,ppm) [a]				ir (ν,cm^{-1})	Formula	Analysis Calcd. (Found)		
	13-H	13a-H	14-H	2-Me			C	H	N
2a	5.31	5.70	8.13		1772,1497	$C_{18}H_{11}N_2O_2Cl$	66.98	3.44	8.68
							(67.33	3.39	8.64)
2b	5.10		5.64	8.14	1736,1498	$C_{22}H_{14}N_2O_2S$	71.33	3.81	7.56
							(71.07	4.03	7.55)
2c		5.91	8.65		1779,1497	$C_{18}H_{10}N_2O_2Cl_2$	60.52	2.82	7.84
							(60.76	2.88	7.95)
2d	5.27	5.60	7.99	2.48	1755,1495	$C_{19}H_{13}N_2O_2Cl$	67.76	3.89	8.32
							(67.60	3.95	8.27)
2e	5.07	5.61	8.07	2.45	1746,1495	$C_{23}H_{16}N_2O_2S$	71.11	4.20	7.29
							(71.11	4.35	7.24)
2f		5.86	8.53	2.48	1778,1501	$C_{19}H_{12}N_2O_2Cl_2$	61.48	3.26	7.55
							(61.84	3.29	7.87)
2g	5.30	5.68	8.08		1760,1493	$C_{18}H_{10}N_2O_2Cl_2$	60.52	2.82	7.84
							(60.90	2.82	8.06)
2h	5.12	5.63	8.12		1748,1497	$C_{22}H_{13}N_2O_2SCl\cdot H_2O$	62.48	3.57	6.62
							(62.88	3.24	6.61)
2i		5.89	8.58		1777,1495	$C_{18}H_9N_2O_2Cl_3$	55.20	2.32	7.15
							(55.40	2.29	7.26)
2j	5.34	6.21	8.10		1756,1480	$C_{18}H_{11}N_2OSCl$	63.81	3.27	8.27
							(63.73	3.27	8.23)
2k	5.14	6.12	8.15		1764,1476	$C_{22}H_{14}N_2OS_2$	68.37	3.65	7.25
							(68.73	3.65	7.29)
2l		5.77	8.27		1800,1486	$C_{18}H_{10}N_2OSCl_2$	57.92	2.70	7.51
							(58.20	2.70	7.49)
2m	5.35	6.20	8.05	2.53	1749,1481	$C_{19}H_{13}N_2OSCl$	64.67	3.71	7.94
							(64.51	3.72	8.06)
2n	5.15	6.14	8.11	2.45	1747,1481	$C_{23}H_{16}N_2OS_2$	68.97	4.03	6.99
							(68.78	4.35	6.65)
2o		5.70	8.11	2.47	1787,1479	$C_{19}H_{12}N_2OSCl_2$	58.92	3.12	7.23
							(58.59	3.34	7.27)
2p	6.13	6.29	8.95		1754,1479	$C_{18}H_{10}N_2OSCl_2$	57.92	2.70	7.51
							(57.61	2.70	7.66)
2q	5.19	6.19	8.16		1766,1481	$C_{22}H_{13}N_2OS_2Cl$	62.77	3.11	6.66
							(63.04	3.09	6.79)
2r		5.74	8.16		1787,1479	$C_{18}H_9N_2OSCl_3$	53.02	2.23	6.87
							(52.81	2.21	6.79)

[a] The 14-H and 2-Me signals appear as singlets; the 13a-proton of 2c,f,i occurs as a sharp multiplet; the corresponding signal appears in 2l,o,r as a singlet.

EXPERIMENTAL

Melting points were determined with a Büchi oil bath apparatus (Kofler hot stage apparatus for 2j,l,p) and are uncorrected. Ir spectra (KBr) were recorded with a Perkin-Elmer 983 spectrophotometer. The ^{1}H nmr spectra were measured with a Varian EM-390 (90 MHz) spectrometer using deuteriochloroform as the solvent (N,N-dimethylformamide-d_7 for 2p) and tetramethylsilane as internal standard. Merck silica gel 60 (230-400 mesh) (1:50) was used for column chromatography. The drying agent was sodium sulphate.

Quino[2,3-b][1,5]benzoxazepines (1a-c) and Corresponding Benzothiazepines (1d-f)

All the title benzoxazepines and benzothiazepines are known (except for the 2-chloro-substituted oxazepine (1c)) and were prepared following the procedure previously described by us. [2,3]

Compound (1c), obtained in 88% yield, had mp 187.5-188 °C (dichloromethane-ethyl acetate); ir: 1612, 1488 cm^{-1}; nmr: δ 8.09 (1H, s, 13-H), 8.55 (1H, s, CH=N). Anal. Calcd for $C_{16}H_9N_2OCl$: C, 68.46; H, 3.23; N, 9.98. Found: C, 68.15; H, 3.40; N, 9.70.

General Procedure for the Preparation of Condensed β-Lactams (**2a-r**)

A mixture of quino[2,3-b][1,5]benzoxazepine (**1a-c**) or benzothiazepine (**1d-f**) (0.5 mmol) and dry Et_3N (1 mmol) in dry benzene (2 ml) was stirred under reflux and the appropriate acid chloride (1 mmol) , dissolved in dry benzene (2 ml), was added dropwise for 15 min. Refluxing and stirring were continued for 1 h, and then the reaction mixture was partitioned between ethyl acetate and water. The organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried and evaporated. Column chromatography of the residue afforded homogeneous 13,13a-dihydro-12H-azeto[2,1-d]quino[2,3-b][1,5]benzoxazepin-12-one (**2a-i**) or corresponding benzothiazepin-12-one derivative (**2j-r**). The following eluents were used: dichloromethane for **2a,g,j,k,m**; n-hexane- dichloromethane (3:7) for **2b,c,d,e,f,h,i,l,o,p,q,r**; n-hexane-dichloromethane (1:9) for **2n**.

Formyl Chloroacetamido Derivatives (**4a,b**)

Imine (**1a** or **1d**) (0.25 mmol) was dissolved in dry benzene (1 ml) and a solution of chloroacetyl chloride (0.5 mmol) in dry benzene (1 ml) was added. The reaction mixture was refluxed for 1 h and then partitioned between ethyl acetate and water. The organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried and evaporated. Crystallization of the residues from ethyl acetate-n-hexane afforded pure title derivatives (**4a,b**).

Compound **4a** had mp 161 °C; ir: 3243, 1695, 1664 cm^{-1}; nmr: δ 4.13 (2H, s, CH_2), 8.84 (1H, s, 4-H), 9.14 (1H, br s, NH), 10.74 (1H, s, CHO). Anal. Calcd for $C_{18}H_{13}N_2O_3Cl$: C, 63.44; H, 3.85; N, 8.22. Found: C, 63.46; H, 3.87; N, 8.04.

Compound **4b** had mp 113.5-114 °C; ir: 3287, 1688, 1668 cm^{-1}; nmr: δ 3.95 (2H, s, CH_2), 8.63 (1H, s, 4-H), 9.55 (1H, br s, NH), 10.50 (1H, s, CHO). Anal. Calcd for $C_{18}H_{13}N_2O_2SCl$: C, 60.58; H, 3.67; N, 7.85. Found: C, 60.60; H, 3.72; N, 7.73.

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