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RING TRANSFORMATIONS OF 1,3-BENZOTHIAZINE DERIVATIVES II.[1,2] CONVERSION OF 6α-ARYL-7α-CHLORO-2,3(2',3'-DIALKOXYBENZO)-1-THIAOCTEMS[3] INTO 2-CARBOMETHOXY-3-ARYL-7,8-DIALKOXY--4,5-DIHYDRO-1,4-BENZOTHIAZEPINES

LAJOS FODOR
Central Laboratory, County Hospital, H-5701 Gyula, POB 46, Hungary

JÁNOS SZABÓ*, ERZSÉBET SZŰCS, GÁBOR BERNÁTH
Institute of Pharmaceutical Chemistry, University Medical School, H-6701 Szeged, POB 121, Hungary

PÁL SOHÁR
Spectroscopic Department, EGYT Pharmacochemical Works, H-1475 Budapest, POB 100, Hungary

JÓZSEF TAMÁS
Central Research Institute of Chemistry, Hungarian Academy of Sciences, H-1525 Budapest, POB 17, Hungary

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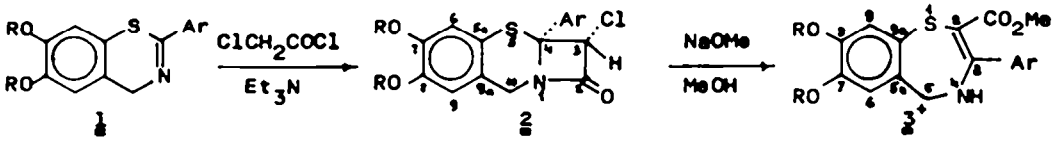
Abstract - 6,7-Dialkoxy-2-aryl-4H-1,3-benzothiazines (1a-g) react with chloroacetyl chloride to give condensed β-lactam derivatives (2a-g). Basic treatment of 2a-g in methanol led to the corresponding 1,4-benzothiazepine derivatives (3a-g) via ring expansion. The structures of the products were determined by IR, NMR and MS studies.

The *in situ* generation of chloroketene was utilized recently[4] for the preparation of the β-lactams (2a-g) from chloroacetyl chloride and a solution of 6,7-dialkoxy-2-aryl-4H-1,3-benzothiazines (1a-g)[5-7] and triethylamine in benzene under reflux. Spectroscopic evidence indicated that all the β-lactam derivatives prepared in this work (2a-g) were stereohomogeneous. The configurations of the compounds (the steric positions of the Cl substituent relative to the four-membered ring) were established by spectroscopic methods.



1 2 3

a: R = OEt; Ar = Ph
b: R = OMe; Ar = o-ClC_6H_4
c: R = OMe; Ar = p-ClC_6H_4
d: R = OMe; Ar = o-MeC_6H_4
e: R = OMe; Ar = p-MeC_6H_4
f: R = OMe; Ar = p-$MeOC_6H_4$
g: R = OMe; Ar = 3,4$(MeO)_2C_6H_3$

Scheme 1

*The numbering of the benzothiazepines 3 in the Title and Abstract is not identical with that used in the text, Tables or Scheme; this is to facilitate comparison of spectroscopically analogous atoms in 2a-g and 3a-g, respectively.

When 2a-g were treated with one molar equivalent of sodium methoxide in methanol they were smoothly transformed to 2-carbomethoxy-3-aryl-7,8-dialkoxy--4,5-dihydrobenzothiazepines (3a-g) (Scheme 1). This ring transformation resembles the ring expansion[8] of 6α-chloropenicillanic acid derivatives to dihydro--1,4-thiazines on treatment with sodium methylate, and it can be assumed that the mechanism of the reaction 2 → 3 is analogous to that suggested for the former process.[8] Further investigations on the reaction mechanism of the ring transformation of 2 and related derivatives bearing other substituents on the azetidinone ring of 1,3-benzothiazine-β-lactams are under way, and the results will be published later.

Table 1. Physical and analytical data on compounds 2a-g and 3a-g

Compound	Yield %	M.p. °C	Formula M.w.	Analysis/% Calcd./Found C	H	N	S
2a	73	111-113	$C_{20}H_{20}ClNO_3S$ 389.89	61.61 62.03	5.17 5.27	3.59 3.85	8.22 8.45
2b	79	179-181	$C_{18}H_{15}Cl_2NO_3S$ 396.28	54.55 54.77	3.81 4.12	3.53 3.33	8.09 8.26
2c	89	184-185	$C_{18}H_{15}Cl_2NO_3S$ 396.28	54.55 54.38	3.81 4.03	3.53 3.29	8.09 8.20
2d	75	156-157	$C_{19}H_{18}ClNO_3S$ 375.86	60.71 61.00	4.83 4.60	3.72 3.86	8.53 8.25
2e	85	176-177	$C_{19}H_{18}ClNO_3S$ 375.86	60.71 61.03	4.83 4.67	3.72 4.02	8.53 8.50
2f	67	179-180	$C_{19}H_{18}ClNO_4S$ 391.86	58.23 58.20	4.63 4.51	3.57 3.66	8.18 8.45
2g	67	174-175	$C_{20}H_{20}ClNO_5S$ 421.89	56.93 56.77	4.78 4.82	3.32 3.12	7.60 7.40
3a	94	149-150	$C_{21}H_{23}NO_4S$ 385.46	65.43 65.12	6.01 5.96	3.63 3.58	- -
3b	97	169-170	$C_{19}H_{18}ClNO_4S$ 391.86	58.23 58.09	4.63 4.67	3.58 3.51	- -
3c	96	170-171	$C_{19}H_{18}ClNO_4S$ 391.86	58.23 58.27	4.63 4.58	3.58 3.62	- -
3d	91	142-143	$C_{20}H_{21}NO_4S$ 371.44	64.67 64.51	5.70 5.62	3.77 3.68	- -
3e	94	143-144	$C_{20}H_{21}NO_4S$ 371.44	64.67 64.75	5.70 5.59	3.77 3.84	- -
3f	90	162-163	$C_{20}H_{21}NO_5S$ 387.44	62.00 62.17	5.46 5.71	3.62 3.57	- -
3g	91	189-191	$C_{21}H_{23}NO_6S$ 417.46	60.42 60.21	5.55 5.47	3.36 3.42	- -

A systematic study of analogous linearly condensed β-lactams of type 2 (R = OMe, Ar = Ph, substituents on C-3: Ph, OPh, Cl and Cl_2) confirmed the configurations (cis positions of the aryl and chloro substituents of the β-lactam ring) given in the Formulae. The configurations were determined by ^1H and ^{13}C NMR investigations, making use of the aromatic solvent-induced shifts.[9]

The practically identical carbon chemical shifts (within 0.3 ppm, except for C-6,9,9a where the shift differences are 3.2, 2.9 and 0.6 ppm) of **2a** and **2** (R = OMe)[9] are clear-cut evidence of the identical configuration of these compounds (the reasonably higher shift differences of C-6,9,9a arise from the different substituents R in positions 7 and 8).

Taking into account the substituent effects of the Ar group, no essential changes are observable for compounds **2b-g**, either. Consequently, the unaltered cis position of this group and of the C-3 chloro atom is plausible. The proposed ring transformation **2** → **3** is revealed by the following spectroscopic observations:

1. The characteristic high-frequency IR carbonyl band (1775-1795 cm^{-1}) of the β-lactams **2a-g** is substituted by the ν C=O band of conjugated ester groups between 1650 and 1670 cm^{-1}.

2. In the IR spectra of compounds **3a-g** ν NH bands are observable in the interval 3390-3280 cm^{-1}.

3. A spin-spin coupling can be detected in the ^1H NMR spectra of **3a-g** through the doublet and triplet splitting of the 5-methylene and NH signals, respectively, due to the presence of a CH_2NH group.

4. Besides the practically unaltered proton signals of the aromatic rings and of their substituents, the ^1H NMR spectra of **3a-g** display the methyl singlet of the carbomethoxy group (3.30-3.45 ppm, of 3H intensity) relative to **2a-g**. Further, the H-3 singlet of 1H intensity is not detectable.

5. In the ^{13}C NMR spectra of **3a-g**, instead of the saturated C-3 and C-4 signals (at 68.0-69.0 and 71.0-72.2 ppm, respectively) for **2a-g**, the lines of olefinic carbons appear at considerably lower fields (C-3: 153.8-157.4; C-2: 89.9-92.1 ppm). The relatively strongly shielded C-2 is characteristic of a conjugated carbonyl group: the mesomerism $C_\alpha=C_\beta-C=\ddot{O}: \leftrightarrow C^{\oplus}-C^{\ominus}=C^{\oplus}-\ddot{O}:^{\ominus}$ shows up in the diamagnetic shift of the C_α(C-2) signal and in an opposite shift of C_β(C-3).[10a]

6. The ring expansion causes a strong paramagnetic shift of the C-5a,9a,10 signals, too, for compounds **3a-g**.

7. In the carbon NMR spectra of **3a-g** there is one more line than in the spectrum of the corresponding β-lactam, and the chemical shift of the additional line lies in the interval (50.8-51.5 ppm) expected for the carbomethoxy derivatives.[10b, 11]

8. It is worth mentioning that the methylene protons in position 5 in compounds **3b** and **3d**, having an ortho-substituted aryl group on C-3, are chemically non-equivalent, whereas in the other benzothiazepines (**3a,c,e-g**) they are equivalent (cf. Table 2). The chemical equivalence of the H-5 atoms is a consequence of fast inversion of the heteroring. This molecular motion is hindered by the steric hindrance between the C-2 carbomethoxy and the C-3 aryl substituents in compounds bearing a bulky ortho-substituted aryl group on C-3. Thus, this fact is further evidence in support of structure **3**.

Mass spectrometric study of **3b-g** also gave results in strong support of the above benzothiazepine structures:

(a) all mass spectra (Table 4) exhibited abundant peaks of molecular ions, the exact masses of which were found to correspond to the chemical formulae listed in Table 1;

(b) most of the fragmentation routes are common or analogous (Scheme 2), and characteristic processes involving contraction of the seven-membered heteroring are observable (SH loss and ArCN elimination);

Table 2. IR and ^{1}H NMR data on compounds 2a-g and 3a-g

No.	IR data (cm^{-1}) in KBr			^{1}H NMR chemical shifts (δ_{TMS} = 0 ppm) in $CDCl_3$ at 250 MHz						
	ν_{NH} band	$\nu_{C=O}$ band[a]	$\gamma_{C_{Ar}H}$ band	CH_2 (2H)[b]	OMe s, (3H) Pos.7,8 (2x3H)	Ar[c]	COOMe	H-3NH (1H)[l]	ArH-6 s(1H)	ArH-9 s(1H)	ArH (Ar group)
2a	-	1775	750 690[d]	4.25 4.90	1.38[e] 1.39[e] 3.98[f] 4.02[f]	-	-	5.12	6.67,	6.68	7.3-7.45 m(5H)
2b	-	1780	755	4.40 5.00	3.78 3.86	-	-	5.27	6.62,	6.73	7.2-7.45 m(4H)
2c	-	1795	845	4.28 4.92	3.81 3.83	-	-	5.11	6.66,	6.67	7.32, 7.40 2xm(2x2H)[g]
2d	-	1785	749	4.35 4.98	3.79 3.82	2.50	-	5.18	6.64,	6.76	7.1-7.3 m(4H)
2e	-	1780	852 810	4.25 4.93	3.80 3.82	2.33	-	5.10	6.66[h]		7.16, 7.35 2xm(2x2H)[g]
2f	-	1785	852 814	4.26 4.91	3.81[i] 3.82[i]	3.78[i]	-	5.09	6.66[h]		6.88, 7.26 2xm(2x2H)[g]
2g	-	1780	-	4.28 4.93	3.83[i] 3.84[i]	3.87[i] 3.91[i]	-	5.12	6.69[h]		6.85, 6.96 2xd(2x1H)[j] 7.02 dd(1H)
3a	3380	1670	755 745[d] 695 685[d]	4.85[k]	1.41[e] 1.43[e] 4.15[f]	-	3.30	4.85[k]	7.15[h]	6.75	7.1-7.4[h,3,g] m(6H)
3b	3330	1670	755	4.75 5.05	3.88 3.90	-	3.45	≈4.5	7.15	6.74	7.1-7.4 m(4H)
3c	3375 3370	1665	840 825	4.90	3.87 3.89	-	3.42	4.55	7.13	6.73	7.12, 7.26 2xm(2x2H)[g]
3d	3380	1670	755	4.82 4.90	3.85 3.87	2.11	3.33	4.65	7.15[h]	6.72	6.9-7.2[h] m(5H)
3e	3375 3365	1665	825	4.88	3.87 3.89	2.32	3.42	4.50	7.15	6.73	7.08 s(4H)
3f	3390 3370	1665 1655	835	≈4.9	3.87[i] 3.89[i]	3.78[i]	3.45	4.55	7.15	6.75	6.8, 7.15 2xm(2x2H)[g]
3g	3280	1650	-	4.90	3.87[i] 3.89[i]	3.80[i] 3.85[i]	3.41	4.65	7.15	6.7-6.8	m(4H)[h]

[a] of β-lactam (2a-g) or of carbomethoxy group (3a-g)

[b] Pos. 10 (2a-g), AB spectrum, J(AB): 16.2 (2a), 16.4 (2b,c,e), 16.5 (2d) and 16.3 Hz (2f,g) or Pos. 5, part A_2 of an A_2X multiplet, J(A,X) ≈5 Hz (3a,c,e-g) or part AB of an ABX multiplet, J(AB) ≈15 Hz, J(AX) J(BX) ≈5 Hz

[c] in 2d,e and 3d,e $C_{Ar}Me$

[d] $\gamma C_{Ar}C_{Ar}$ band characteristic of mono-substituted benzene ring

[e,f] CH_3, t(3H) and CH_2 qa (2H) signals of OEt groups in Pos. 7,8 (J ≃ 7 Hz)

[g] part A or B of an AA'BB' multiplet J(AB) ≈8.5 Hz

[h,k] two overlapping signals

[i] alternative assignment is also possible

[j] J = 8.4 and 2.0 Hz

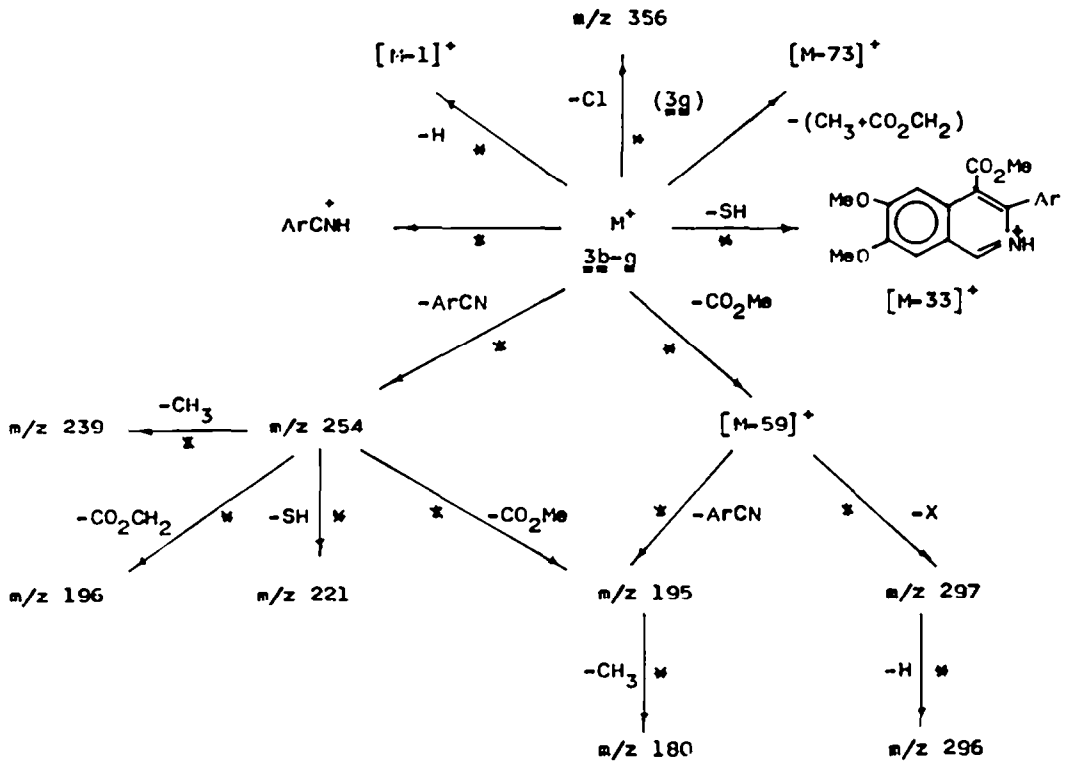
[l] H-3 (2a-g), s or HN (3a-g), broad t

Table 3. ^{13}C NMR chemical shifts (δ_{TMS} = 0 ppm) of compounds 2a-g, 3a-g in $CDCl_3$ solution at 20.14 MHz

No.	C=O[a]	C-3	C-4/2[b]	C-5a	C-6,9		C-7,8		C-9a	C-10/5	OCH_3(7,8)[c]	CH_3 Ar/Et	C-1'	C-2'	C-6'	C-3'	C-5'	C-4'
2a	164.4	68.6	71.4	120.4	114.4	115.3	148.3	149.1	122.5	43.1	65.1[d] 65.2[d]	14.7 14.8	137.0		126.9	128.4		128.9
2b	164.7	68.5	71.2	121.2	111.7	112.8	148.5	149.5	121.5	43.6	56.2 56.4	-	136.1	132.8	127.3	130.0[e]	126.7	130.8[e]
2c	164.2	68.3	71.0	120.3	112.0	113.3	148.8	149.4	122.1	43.2	56.3[f]	-	135.6[e]		128.5[g]	128.7[g]		135.2[e]
2d	164.8	68.1	72.2	120.8	111.8	113.0	148.4	149.2	123.2	44.0	56.1 56.2	21.1	135.5	136.0	125.8[f]		128.8[e]	131.8[e]
2e	164.4	68.6	71.4	120.7	111.9	113.1	148.5	149.2	122.2	43.0	56.2[f]	21.1	133.8		126.9	129.1		138.9
2f	164.4	68.8	71.2	120.8	111.9	113.1	148.5	149.2	122.1	42.9	56.3[f] 55.3[c]	-	128.7		128.5	113.9		160.2
2g	164.5	69.0	71.5	121.0	111.6[f]		148.8[e]	149.5[e,f]	122.5	43.1	56.1[g] 56.4[g] 56.5[c,f,g]	-	129.4	113.4	120.0	149.5[f,e]	112.3	150.2
3a	168.0	157.1	90.7	135.5	114.6	118.1	149.0	149.1	130.0	49.0	65.0[d] 65.4[d] 51.1[h]	14.9[f]	141.4		127.5	128.1		128.7
3b	166.8	153.8	92.1	135.3	111.8	116.1	149.2	149.4	129.5	49.0	56.4[f] 51.5[h]	-	139.8	132.0	129.5[f]	129.2	126.6	129.5[f]
3c	167.6	155.7	91.4	135.3	111.8	116.1	149.3	149.4	129.4	49.1	56.3[f] 51.4[h]	-	139.6		129.0	128.4		134.8
3d	166.9	156.5	89.9	135.3	111.6	115.6	148.7	149.0	129.5[f]	48.4	55.9 56.0 50.8[h]	18.3	140.4	134.7	126.8[e]	127.8[g]	125.2[e]	129.5[f,g]
3e	167.9	157.4	89.6	135.3	111.8	115.7	148.8	149.0	129.6	48.7	56.0[f] 50.9[h]	21.0	138.4[e]		127.2[g]	128.6[g]		138.9[e]
3f	168.1	157.2	90.1	135.5	112.0	115.9	149.1	149.3	129.8	49.0	56.2[f] 51.2[h] 55.2[c]	-	133.6		128.9	113.5		160.2
3g	168.1	156.8	90.2	135.3	111.9[e]	115.8	149.0[g]	149.1[g]	129.7	48.9	56.2[f,i] 51.2[h] 55.8[i] 56.0[i]	-	133.8	111.4[e]	120.1	148.7[g]	110.9[e]	149.7[g]

[a] C-2 (2a-g) or C-10 (3a-g)
[b] C-4 (2a-g) or C-2 (3a-g)
[c] or in Ar groups
[d] OCH_2 in O-ethyl groups
[e,g,i] reversed assignment is also possible
[f] overlapping lines
[h] $COOCH_3$ groups

(c) significant ortho-effects were observed, especially on the primary loss of a Cl atom of the Ar group and on the abundances of $[M-59]^+$ and $[M-73]^+$ ions for the isomeric pairs (3b-c and 3d-e).



*denotes a substituent of the Ar group

*processes supported by 1st or 2nd FFR metastable peaks

Scheme 2

EXPERIMENTAL

The IR spectra were run on a Specord 75 (JENA) grating spectrometer, in KBr pellets. ^{1}H NMR spectra were recorded at room temperature in $CDCl_3$ solution at 250 MHz, on a BRUKER WM-250 FT spectrometer equipped with a superconducting magnet, using TMS as internal standard. The mass spectra of normal and metastable ions were taken and the exact mass measurements were carried out using an AEI MS-902 double focusing instrument with a direct inlet system. Operating conditions: 8 kV, 70 eV, 160 °C source temperature.

General procedure (for 2a-g and 3a-g). Compounds 1a-g (0.01 mol) and chloroacetyl chloride (0.01 mol) were dissolved in benzene and Et_3N (0.01 mol) was added dropwise, with stirring, during 1 h. The crystalline $Et_3N.HCl$ was removed by filtration, the benzene solution was evaporated, and the residue was crystallized from EtOH to yield colourless crystals (2a-g, cf. Table 1).

Compounds 2a-g (0.01 mol) were dissolved in methanol and sodium methoxide (0.01 mol) was added. The solution was stirred under reflux. After 3 h the solution was diluted with chloroform and extracted with water. The organic layer was dried (Na_2SO_4) and evaporated and then crystallized from MeOH to yield crystals (3a-g, cf. Table 1).

Table 4. Main selected ions in the 70 eV mass spectra of 3b-g

Ions	Relative abundances (B %)					
	3b	3c	3d	3e	3f	3g
M^+	60	61	63	60	61	84
$[M-1]^+$	12	8	13	7	6	10
m/z 356	24					
$[M-33]^+$	100	100	100	100	100	100
$[M-59]^+$	16	54	38	60	65	57
$[M-73]^+$	4	24	5	28	27	45
m/z 297	76	23	16	8	15	26
m/z 296	75	26	17	12	19	25
m/z 254	9	23	6	20	40	36
m/z 239	14	17	10	12	17	15
m/z 221	7	11	4	6	9	12
m/z 196	19	33	6	23	22	18
m/z 195	32	54	10	40	51	42
m/z 180	9	14	4	11	9	7
$[ArCNH]^+$	13	13	8	16	23	18

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