Investigation of ring transformations of diaryl-β-lactams condensed with 1,3-benzothiazines

Lajos Fodor, a,b,c Péter Csomós, a,b,c Benedek Károlyi, d Antal Csámpai, d and Pál Sohár* d

aInstitute of Health Care and Environmental Sanitation Studies, Szent István University, H-5700, Gyula, Szent István st. 17–19;
 bCentral Laboratory, County Hospital, H-5701, Gyula, POB 46, Hungary;
 cInstitute of Pharmaceutical Chemistry, University of Szeged, and Research Group of Stereochemistry of the Hungarian Academy of Sciences, H-6720, Szeged, Eőtvös u. 6., Hungary;
 dInstitute of Chemistry, Eőtvös Loránd University, H-1518 Budapest, POB 32, Hungary

E-mail: Synthesis: fodor@pandy.hu  Spectroscopy: sohar@chem.elte.hu

Dedicated to Professor Ferenc Fülöp on the occasion of his 60th birthday

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Abstract
Reactions of derivatives of the isoquinoline analog trans-2,2a-diaryl-2,2a-dihydro-5,6-dimethoxy-1H,8H-azeto[2,1-b][1,3]benzothiazin-1-one were studied under basic conditions. Their treatment with sodium methoxide in methanol resulted first in alcoholsysis of the β-lactam ring, followed by opening of the thiazine ring and oxidation of the thiol moiety to disulfide. Thus, the corresponding β-amino acid derivatives, disulfides of N-(ortho-mercaptobenzyl)-substituted diaryl-3-aminoacrylic acid methyl esters, were obtained in good yields. The structures of the new molecules were proved by means of NMR and IR spectroscopy. Geometric isomerism investigations indicated the presence of the Z forms of the acrylic acid moiety.

Keywords: 1,3-Benzothiazine, β-lactam, β-amino acid, 3-aminoacrylic acid, ring opening, disulfide

Introduction
There has recently been a rapid increase in research interest in β-lactams from both medical and chemical aspects.1–8 A considerable proportion of drugs contain an azetidinone ring (e.g. β-lactam antibiotics and taxol derivatives).2 Besides their inestimable pharmacological effects, β-lactams play a crucial role as intermediates in the preparation of many molecules.1–8

Starting from β-lactams, a wide variety of β-amino acids can be obtained,3 including
enantiopure β-amino acids prepared by the direct or indirect enzymatic treatment of β-lactams. They are good starting materials for functionalized β-amino acids, various chiral catalysts and β-peptides. Many heterocycles have been prepared from compounds containing an azetidinone ring.

In the course of our recent studies on S- and N-containing condensed-skeleton heterocycles, we investigated reactions of 1,3- and 3,1-benzothiazines condensed with a β-lactam ring (Figure 1). The ring expansion of monochloroazeto[2,1-b][1,3]benzothiazin-1-ones 1 with sodium methoxide afforded 1,4-benzothiazepines 4 as single products in good yields (path A). When the aryl substituent of 1 contained an ortho-nitro group, an excess of sodium methoxide in methanol yielded indolo-1,4-benzothiazepines 5 via a novel rearrangement (path B). Basic treatment of dichloro-β-lactam condensed-1,3-benzothiazines 1 provided three interesting heterocyclic products: 1,4-benzothiazepines 4, isoquinolines 6 and thiazoles 7 (path C). The reactions of 1,3-benzothiazines angularly condensed with a β-lactam ring 2 were also studied in the presence of sodium methoxide. The dichloro-β-lactam ring of 2 proved to be useful protection strategy for the synthesis of 4-aryl-2H-1,3-benzothiazine 1,1-dioxides (path D). After the oxidation of 1,1-dichloroazeto[2,1-c][1,3]-benzothiazin-2-ones 2, the thiazine ring could be recovered selectively and in good yield by treatment with sodium methoxide (path D). A series of aryl-substituted β-lactams condensed with 1,3-benzothiazines and isoquinolines 2 were isomerized in the presence of sodium methoxide to the thermodynamically more stable form 9 (path E). The ring transformations of (2R*,2aS*)-2-chloro-2a-aryl-2a-dihydro-2H,4H-azeto[1,2-a][3,1]benzothiazin-1-ones 3 with sodium ethoxide in ethanol provided variously substituted (R*)-3-ethoxycarbonyl-2-aryl-3,5-dihydro-4,1-benzothiazepines 10 and 3-ethoxycarbonyl-2-aryl-1,5-dihydro-4,1-benzothiazepines 11 (path F). Surprisingly, the tautomers obtained could be separated by column chromatography and proved unexpectedly stable in solution; 10 and 11 exhibit the rare phenomenon of desmotropy. As a continuation of such studies, we were interested in the reactivity of azeto[2,1-b][1,3]benzothiazin-1-ones 2, and set out to investigate their reactions with sodium methoxide in methanol (path G).

Results and Discussion

For the preparation of 2,2a-diaryl-2,2a-dihydro-5,6-dimethoxy-1H,8H-azeto[2,1-b][1,3]benzothiazin-1-ones 13a–f (Scheme 1), we subjected 2-aryl-2H-1,3-benzothiazines 12a–f to the Staudinger reaction with substituted phenylacetyl chlorides in refluxing toluene. In these reactions, only one isomer was obtained selectively, as described earlier for 13a. Thus, isomers of 13a–f were formed in which 2-Ar is cis to 2a-Ar. Treatment of 13a–f with two equivalents of sodium methoxide in refluxing methanol in each case provided only one product, 17a–f, as revealed by NMR spectroscopy.

As concerns the mechanism (Scheme 1), the first step in this reaction is most probably alcoholsysis of the β-lactam ring of 13, resulting in diphenyl ester 14. The thiazine ring of 14...
can be further transformed to the corresponding chain intermediate 15. This latter imine 15 converts to an enamine, providing an acrylic acid derivative 16, which is followed by oxidation to disulfide 17 by air.

Figure 1. Transformations of various β-lactam-condensed 1,3-benzothiazines.

The IR, $^1$H- and $^{13}$C-NMR spectral data (Tables 1 and 2) furnish unambiguous proof of the presumed structures of the new compounds 13b–f and 17a–f. Merely the following comments are necessary.

The presence of the azetidinone ring in compounds of type 13 is obvious from the νC=O IR band in the expected interval, $^{16a}$ 1762–1777 cm$^{-1}$, and the carbon line with chemical shifts 169.0–170.1 ppm, also in accordance with the literature data.$^{17a}$

The assignment of the carbon line and the position of the oxo group are confirmed by the cross peaks with the methylene hydrogens H’s in the 2D-HMBC spectra.

The H-2 chemical shifts of 13d and 13e are higher (4.90 and 5.08 ppm) than those of 13b,c,f (4.81–4.84 ppm) due to the ortho substituent on the benzene ring attached to C-2′. As a
consequence of the steric hindrance between the two aromatic rings (on C-2 and C-2’) the C-2 substituent is forced into an orientation in which H-2 is coplanar with the benzene ring on C-2. The parallel orientation of the benzene rings on C-2 and C-2’ and their position cis to the azetidinone ring are confirmed by the mutual anisotropic effects on the aromatic H’s, as described earlier for 13a. As a consequence, the chemical shifts of the H’s mentioned above are ~7 ppm for the cis isomers, while for the trans counterparts they are downfield-shifted by 0.55–0.70 ppm.

\[\text{Scheme 1. Synthesis of 3-aminoacrylic acid derivatives.}\]

Since the signals of the aromatic H’s appear in the interval 6.78–7.16 in the spectra of 13b–f (except for that on the C-2 nitro-substituted ring on C-2’ in 13e, where the –f effect of the nitro group results in a significant downfield shift), the cis position of the two benzene rings is obvious.

The postulated open-chain structure of 17a–f is proved by the characteristic spectral data on the carbomethoxy group: νC=O (β-enaminoesters\textsuperscript{18}, ν\textsubscript{as}C–O and ν\textsubscript{s}C–O IR bands\textsuperscript{16b} (1634–1638, 1249–1257 and 1039–1161 cm\textsuperscript{-1}), the OCH\textsubscript{3} singlet in the \textsuperscript{1}H-NMR spectrum (3.61–3.64 ppm,\textsuperscript{17b} for 17d 3.48 ppm) and the carbon lines of the OMe and C=O groups (51.3–51.4 ppm\textsuperscript{17c} and 170.2–171.1 ppm\textsuperscript{17a}).

Further proof is given by the lines of the unsaturated carbons between the NH and the ester groups (C-2: 159.8–163.8 ppm and C-2’: 97.2–99.6 ppm) and the NH signal in the IR (3285–
3290 cm\(^{-1}\)) and in the \(^1\)H-NMR spectrum (9.56–9.65 ppm), and also the couplings of the H’s in the CH\(_2\)NH moiety, resulting in doublet and triplet splits, respectively, of the CH\(_2\) and NH signals.

**Table 1.** Characteristic IR frequencies\(^a\) and \(^1\)H NMR data\(^b\) of compounds 13b–f and 17a–f.\(^{c,\ast}\)

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<th>Compound band</th>
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<th>Pos. 5 Pos. 6 2 x (d)</th>
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\(^\ast\) The numbering of the 13-type compounds was used also for 16a–f.
\(^a\) In KBr discs (cm\(^{-1}\)), \(^b\) In CDCl\(_3\) solution (DMSO-d\(_6\) for 17d) at 500 MHz. Chemical shifts in ppm (\(\Delta\)TMS = 0 ppm), coupling constants in Hz. Further signals:
\(\nu\)NH IR band: 3285–3290 (17a–e) and 3275 cm\(^{-1}\) (17f); \(\nu\)asC–O and \(\nu\)sC–O IR bands (17a–f): 1249–1257 and 1039–1161 cm\(^{-1}\); (Ar)CH\(_3\): 2.18 (13f), 2.23 (17f); OCH\(_3\): 3.64 (17a), 3.62 (17b,c), 3.48 (17d), 3.61 (17e,f); NH, \(t\) (1H): 9.65 (17a–d,f); 9.56 (17e); \(^c\) Assignments were supported by HMBC (except for 13b) and HMBC measurements (except for 17d); \(^d\) Condensed benzene ring; \(^e\) p-; for 13d and 17d o-disubstituted ring; \(^f\) Phenyl ring, for 13e and 17e \(\gamma\)C\(_3\)H band of o-disubstituted ring. Two further bands at 783 and 738 cm\(^{-1}\) (17a); \(^g\) 2 x \(d\) (2 x 1H), \(J\): 16.1 (13b,c,f), 16.4 (13d,e), \(d\) (2H), \(J\): 6.2 (17a–c,f, enamine), \(~s\) (2H): ~3.72 (17d, imine), 2 x \(dd\) (2 x 1H), enamine: 3.66, 3.98 (17d), \(J\): 14.7, 5.8 and 5.8 (17e); \(^h\) 1H (13b–f), CH\(_3\) (3H, ester group) for 17a–f; \(^i\) Attached to CH or COO; \(^k\) Attached to C\(_{\text{quat}}\), or CNH; \(^l\) \(dd\), \(t\) (2 x 2H) due to \(^3\)J(H,H) and \(^4\)J(F,H), \(^3\)J(F,H) couplings; \(^m\) H–6’; \(^o\) H–5’, H–3’; 7.88; \(^p\) Overlapping signals; \(^t\) In overlap with the H-4’ of Ar\(^1\).
Due to free rotation around the S–S and C–N bonds the methylene H’s are chemically equivalent in the compounds of type 17 in contrast with 13b–f. The only exception is 17e, in which the ortho-nitro substituent hinders this motion and the methylene H’s become non-equivalent in this crowded molecule.

It should be noted that 17b is poorly soluble in CDCl₃ and we measured the NMR spectra in DMSO-d₆. In this solution, a better-soluble contamination gives well-identifiable signals in the ¹H-NMR spectrum.

Table 2. ¹³C NMR chemical shifts of compounds 13b–f and 17a–f

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<th>C-5</th>
<th>C-6</th>
<th>C-7</th>
<th>2C₃-7a</th>
<th>2C₆-7a</th>
<th>2C₅b(1')</th>
<th>2C₇b</th>
<th>2C₆b</th>
<th>2C₅c</th>
<th>C-meta</th>
<th>C-para</th>
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a In ppm (δTMS = 0 ppm) at 125.7 MHz. Solvent: CDCl₃ (DMSO-d₆ for 17d). Further signals, CH₃: 21.4 (13f), 21.6 (17f); (COO)CH₃: 51.3 (17a–d, f), 51.4 (17e); 2’-Ar, C–2: 131.9 (13d), 132.5 (17d), C-3: 128.05 (13d), 129.8 (17d); b Assignments were supported by DEPT, 2D-HMQC (except for 13b) and 2D-HMBC (except for 17d) measurements; c This numbering was used also for compounds 17a–f; d Reversed assignments is also possible; e, g, h ‘‘Two overlapping lines; f Due to C,F-coupling d [Hz], J: 247.0 (13e), 244.4 (17c), 2: 21.7 (13e), 21.1 (17e), 3: 8.3 (13c), 7.9 (17e), J: < 1 (13c), 3.5 (17c).
Conclusions

The reactions of diarylazeto[2,1-b][1,3]benzothiazin-1-one derivatives with sodium methoxide in methanol provided N-substituted 3-aminoacrylic acid derivatives in Z forms. The reactivity of β-lactams 13a–f in the presence of base differs from that of other isomeric lactams investigated earlier.9–15

Experimental Section

General. Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyzer. The mass spectra were recorded in the interval 200-2200 m/z on an Agilent 1100 LCMSD trap instrument equipped with an electrospray source. Merck Kieselgel 60F254 plates were used for TLC, and Merck Silica gel 60 (0.063-0.100) for column chromatography. Substituted phenylacetyl chloride derivatives were purchased from Aldrich. 1,3-Benzothiazines 12a–f19 and β-lactam 13a15 were prepared earlier. The 1H- and 13C-NMR spectra were recorded in CDCl3 solution in 5-mm tubes at room temperature, on a Bruker DRX 500 spectrometer at 500 (1H) and 126 (13C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The standard Bruker micro program NOEMULT.AU to generate NOE was used with a selective preirradiation time. DEPT spectra were run in a standard manner, using only the Θ = 135º pulse to separate CH/CH3 and CH2 lines phased "up" and "down", respectively. The 2D-HSC and HMBC spectra were obtained by using the standard Bruker pulse programs.

General procedure for diaryl β-lactam derivatives (13b–f)

1,3-Benzothiazines 12b–f (5 mmol) were dissolved in toluene (30 ml), followed by addition of the appropriate substituted phenylacetyl chloride (5 mmol). The mixture was refluxed, and a solution of triethylamine (0.50 g, 5 mmol) in toluene (30 ml) was added dropwise, with stirring, during 1 h. The crystalline triethylamine hydrochloride was removed by filtration, the toluene solution was evaporated and the residue was crystallized and recrystallized from ethanol to obtain white crystals.

2-(4-Chlorophenyl)-2a-phenyl-2,2a-dihydro-5,6-dimethoxy-1H,8H-azeto[2,1-b][1,3]benzothiazin-1-one (13b). White crystalline powder, m.p.: 170–173 ºC (from EtOH); yield 92%. Anal. Calcd. for C24H20ClNO3S (437.94): C, 65.82; H, 4.60; N, 3.20; S, 7.32. Found: C, 65.66; H, 4.72; N, 3.45; S, 7.50. MS(ESI+) [M+1]+ = 438.0

2-(4-Fluorophenyl)-2a-phenyl-2,2a-dihydro-5,6-dimethoxy-1H,8H-azeto[2,1-b][1,3]benzothiazin-1-one (13c). White crystalline powder, m.p.: 163–165 ºC (from EtOH); yield 95%. Anal. Calcd. for C24H20FNO3S (421.48): C, 68.39; H, 4.78; N, 3.32; S, 7.61. Found: C, 68.58; H, 4.85; N, 3.52; S, 7.38. MS(ESI+) [M+1]+ = 422.0
2a-(2-Chlorophenyl)-2-phenyl-2,2a-dihydro-5,6-dimethoxy-1H,8H-azeto[2,1-b][1,3]benzothiazin-1-one (13d). White crystalline powder, m.p.: 222–225 °C (from EtOH); yield 90%. Anal. Calcd. for C_{24}H_{22}ClN_O_S (437.94): C, 65.82; H, 4.60; N, 3.20; S, 7.32. Found: C, 65.58; H, 4.80; N, 3.48; S, 7.55. MS(ESI+) [M+H]^+ = 438.0

2-(4-Chlorophenyl)-2a-(2-nitrophenyl)-2,2a-dihydro-5,6-dimethoxy-1H,8H-azeto[2,1-b][1,3]benzothiazin-1-one (13e). White crystalline powder, m.p.: 226–230 °C (from EtOH); yield 92%. Anal. Calcd. for C_{25}H_{23}ClN_O_S (451.97): C, 66.44; H, 4.91; N, 3.10; S, 7.10. Found: C, 66.73; H, 5.18; N, 2.86; S, 7.36. MS(ESI+) [M+H]^+ = 452.0

General procedure for 3-aminoacrylic acid derivatives (17a–f)

Azeto-1,3-thiazines 13a–f (2.8 mmol) were dissolved in dry methanol (100 ml). To this stirred solution, sodium methoxide (300 mg, 5.6 mmol) was added and the reaction mixture was stirred under reflux for 2 h. After evaporation to 30 ml, the solution was left to stand overnight at room temperature. The crystals that separated out were filtered off and recrystallized from methanol to give 3-aminoacrylic acid derivatives 17a–f as white crystalline products.

2,2′-Di-[(Z-1′′,2′′-diphenyl-2′′-methoxycarbonylvinyl)aminomethyl]-4,4′,5,5′-tetramethoxypiphenyl disulfide (17a). White crystalline powder, m.p.: 159–161 °C (from MeOH); yield 75%. Anal. Calcd. for C_{30}H_{28}N_O_S (869.06): C, 69.10; H, 5.57; N, 3.22; S, 7.38. Found: C, 68.82; H, 5.75; N, 3.48; S, 7.62. MS(ESI+) [M+H]^+ = 869.2; [M+K]^+ = 907.2

2,2′-Di-[(Z-1′′-phenyl-2′′-(4-chlorophenyl)-2′′-methoxycarbonylvinyl)aminomethyl]-4,4′,5,5′-tetramethoxypiphenyl disulfide (17b). White crystalline powder, m.p.: 181–184 °C (from MeOH); yield 82%. Anal. Calcd. for C_{30}H_{46}ClN_O_S (937.95): C, 64.02; H, 4.94; N, 3.00; S, 6.84. Found: C, 64.41; H, 5.17; N, 3.09; S, 7.11. MS(ESI+) [M+H]^+ = 937.1; [M+K]^+ = 975.2

2,2′-Di-[(Z-1′′-phenyl-2′′-(4-fluorophenyl)-2′′-methoxycarbonylvinyl)aminomethyl]-4,4′,5,5′-tetramethoxypiphenyl disulfide (17c). White crystalline powder, m.p.: 178–181 °C (from MeOH); yield 79%. Anal. Calcd. for C_{30}H_{46}ClN_O_S (905.04): C, 66.35; H, 5.12; N, 3.10; S, 7.09. Found: C, 66.12; H, 5.44; N, 3.28; S, 7.31. MS(ESI+) [M+H]^+ = 905.2; [M+K]^+ = 943.2

2,2′-Di-[(Z-1′′-(2-chlorophenyl)-2′′-phenyl-2′′-methoxycarbonylvinyl)aminomethyl]-4,4′,5,5′-tetramethoxypiphenyl disulfide (17d). White crystalline powder, m.p.: 217–220 °C (decomp.) (from MeOH); yield 74%. Anal. Calcd. for C_{30}H_{46}ClN_O_S (937.95): C, 64.02; H, 4.94; N, 3.00; S, 6.84. Found: C, 64.15; H, 5.24; N, 3.18; S, 7.02. MS(ESI+) [M+H]^+ = 937.1; [M+K]^+ = 975.2

2,2′-Di-[(Z-1′′-(2-nitrophenyl)-2′′-(4-chlorophenyl)-2′′-methoxycarbonylvinyl)aminomethyl]-4,4′,5,5′-tetramethoxypiphenyl disulfide (17e). White crystalline powder, m.p.: 216–220 °C (decomp.) (from MeOH); yield 71%. Anal. Calcd. for
C_{50}H_{44}Cl_{2}N_{4}O_{12}S_{2} (1027.94): C, 58.42; H, 4.31; N, 5.45; S, 6.24. Found: C, 58.28; H, 4.60; N, 5.71; S, 6.33. MS(ESI+) [M+1]^+ = 1027.2; [M+Na]^+ = 1049.2

2,2'-Di-((Z-1'-(4-methylphenyl)-2''-(4-chlorophenyl)-2''-methoxycarbonylvinyl)amino-methyl]-4,4',5,5'-tetramethoxydiphenyl disulfide (17f). White crystalline powder, m.p.: 212–215 °C (decomp.) (from MeOH); yield 69%. Anal. Calcd. for C_{52}H_{50}Cl_{2}N_{2}O_{8}S_{2} (966.00): C, 64.65; H, 5.22; N, 3.00; S, 6.64. Found: C, 64.49; H, 5.41; N, 3.20; S, 6.86. MS(ESI+) [M+1]^+ = 965.2; [M+K]^+ = 1004.2.

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