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Simple and Condensed β-Lactams. Part 29[1]. Synthesis and Base-Catalyzed Ring Transformation of 4-[(2*RS*,3*SR*)-3-Hydroxy-1-(4-methoxyphenyl)--4-oxoazetidin-2-yl)]thiazol-2(3*H*)-one[†]

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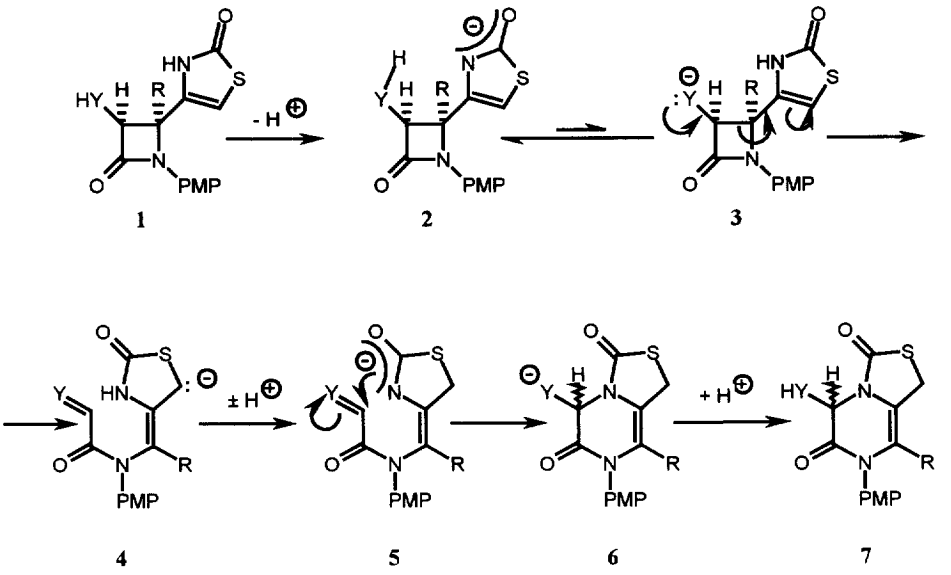
Abstract: 4-[(2*RS*,3*RS*)-3-Hydroxy- (**1b**) and -3-(4-chlorophenoxy)-1-(4-methoxyphenyl)-4-oxo-azetidin-2-yl]thiazol-2(3*H*)-one (**16b**) were synthesised. While the former was smoothly rearranged into (5*RS*)-5-hydroxy-7-(4-methoxyphenyl)-1,5-dihydrothiazolo[3,4-*a*]pyrazine-3,6(7*H*)-dione (**7b**) on treatment with Na_2CO_3 under mild conditions, the latter was found to be stable to Na_2CO_3 under the same conditions. The structural prerequisites for type **1** → **7** ring transformations, including cleavage of the 3-4 bond (azetidin-2-one numbering) of the β-lactam ring are defined.

In part 22[2] of the present series the novel smooth, base-catalyzed ring transformation of amino compound **1a** into the 1,5-dihydro-3*H*-thiazolo[3,4-*a*]pyrazine-3,6(7*H*)-dione (**7a**) was reported. A characteristic feature of the ring transformation was cleavage of the 3-4 bond of the β-lactam ring which is quite rarely observed in β-lactam chemistry.[3] The mechanism shown in Scheme 1 was suggested for ring transformation **1a** → **7a**. It should be noted that anion **3a** is not necessarily a discrete intermediate: deprotonation of the HY (= H_2N) group and cleavage of the 3-4 β-lactam bond could as well take place in a concerted manner.

[†] Dedicated to Prof. Dr. Dietrich Döpp, Duisburg, Germany, on the occasion of his 60th birthday on July 18, 1997



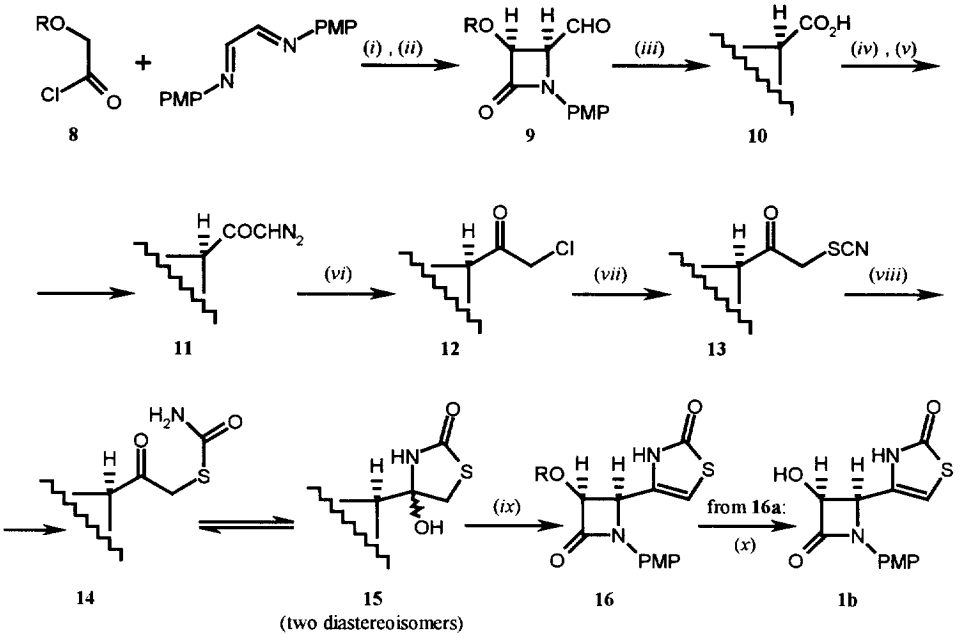
a: Y = NH, R = Me; **b**: Y = O, R = H

Scheme 1. Mechanism of ring transformations **1** → **7**. All compounds are racemic, only one enantiomer is shown; PMP = 4-methoxyphenyl

The necessary condition of the ring transformation including cleavage of the 3-4 bond (azetidin-2-one numbering) appears to be the presence of a sufficiently acidic group HY at position 3 and of another group also containing an acidic hydrogen atom *and* capable of accommodating a negative charge at position 4. This suggests that by suitable modifications and/or replacement of the amino group and the thiazolone moiety further compounds capable of undergoing the novel ring transformation could be designed.

Here we report the synthesis (Scheme 2) of the hydroxy demethyl analogue **1b** of amino compound **1a** and its transformation into compound **7b** on treatment with base.

Reaction of acetoxyacetyl chloride (**8a**) with *N,N'*-bis(4-methoxyphenyl)ethanediimine[4] in dichloromethane in the presence of triethylamine, followed by treatment with hydrochloric acid afforded carbaldehyde **9a**. This was oxidized with $KMnO_4$ and the resulting carboxylic acid **10a** was treated successively with $SOCl_2$ and diazomethane to afford diazomethyl ketone **11a**. The latter was converted by successive treatment with hydrochloric acid and KSCN into thiocyanatomethyl ketone **13a** *via* chloromethyl



a: R = Ac; **b**: R = 4-ClC_6H_4

Scheme 2. Synthesis of compounds **1b** and **16b**; all compounds are racemic, only one enantiomer is shown; PMP = 4-methoxyphenyl. (*i*): Et_3N, CH_2Cl_2, -10°C → r.t.; (*ii*): 1 N HCl; (*iii*): $KMnO_4$, acetone-water; (*iv*): $SOCl_2$, reflux; (*v*): CH_2N_2, THF, r.t.; (*vi*): HCl-Et_2O, CH_2Cl_2, r.t.; (*vii*): KSCN, NaI, dry DMF, 80°C; (*viii*): H_2SO_4, H_2O, -5 - 0°C; (*ix*): AcOH, reflux; (*x*):1 N HCl, MeOH, reflux

ketone **12a**. Addition of one molecule of water to the thiocyanato group (effected by treatment with sulfuric acid) afforded initially what was shown by TLC to be a mixture of *three* compounds. When the mixture was subjected to flash chromatography the least polar component completely disappeared. Similarly, in the ^1H- and ^{13}C-NMR spectra of the original *three*-component product only *two* compounds, *viz.* the two diastereoisomeric ring forms **15a** were seen. Earlier the analogue of compound **13a** (with a phthalimido group replacing the acetoxy group and a methyl group replacing 2-H of the oxoazetidin-2-yl group) had been found to add one molecule of water to afford what was shown by NMR to be the corresponding analogue of compound **14a** (without any contamination by its ring tautomers);[2] moreover, addition of water to compound **13b** was also found to afford the open-chain tautomer **14b** (see below). In consequence we believe that in the

acetoxy series the tautomeric equilibrium is completely shifted towards the two diastereoisomeric forms **15a** and that the least polar component of the original hydration product of compound **13a** may reasonably be assigned the unstable open-chain structure **14a**.

When refluxed with acetic acid, the tautomeric mixture of the hydration products of compound **13a** was dehydrated to afford compound **16a** which was subsequently deacetylated by prolonged refluxing with 1N HCl in methanol to afford compound **1b**.

While the rather vigorous conditions of the deacetylation step demonstrate that the resulting compound **1b** is stable to acid, its rearrangement into compound **7b** was smoothly brought about by treatment with base under mild conditions (Na_2CO_3, aqueous methanol, r.t.). The same treatment of acetoxy derivative **16a** furnished, as expected, compound **7b** directly.

Similarly obtained, starting with (2*RS*,3*RS*)-3-(4-chlorophenoxy)-1-(4-methoxyphenyl)-4-oxo-azetidine-2-carboxylic acid (**10b**)[5], was compound **16b**; the only difference between the **a** and **b** series was that, in the latter series, the water adduct of compound **13b** was shown by its ^{1}H-NMR and mass spectra to possess the open-chain tautomeric structure **14b** (see Experimental). Compound **16b** proved stable to base under conditions under which compounds **1b** (and **16a**) are smoothly rearranged into compound **7b**. This proves that the presence of a sufficiently acidic group HY attached to C-3 of the β-lactam ring is indeed a necessary prerequisite for the ring transformation to occur; its replacement by an RY group carrying one or more unshared electron pairs on Y results in loss of the instability to base.

Experimental

Dichloromethane will be abbreviated as DCM. $MgSO_4$ was invariably used as the drying agent. Evaporations to dryness were carried out at reduced pressures (*ca* 2.5 kPa).

Separations of product mixtures by column chromatography (c.c.) were mostly carried out at reduced pressures (10-25 kPa) using Kieselgel G 60 (Merck) as the adsorbent. For preparative t.l.c. separations 20 x 20 cm glass plates coated with Kieselgel $PF_{254+366}$ (Merck; thickness of adsorbent layer 1.5 mm) were used. The solvents used are given in parentheses. The purity of the products was checked, in combination with IR spectroscopy, by t.l.c. on DC-Alufolien 60 F_{254} (Merck); the individual compounds were detected by UV irradiation or by using iodine, 5 % ethanolic molybdo- or tungstophosphoric acids as the reagents.

Melting points were determined on a Kofler hot-stage m.p. apparatus. IR spectra were recorded on a Specord-75 (Zeiss, Jena) spectrometer, ^{1}H and ^{13}C n.m.r. spectra were obtained with Varian VXR-400 or, where noted, with Bruker AW 80 spectrometers in $CDCl_3$-DMSO-d_6 solutions, unless otherwise stated, and using tetramethylsilane as the internal reference compound; *J* values (approximate *J* values for the 80 MHz

spectra) are given in Hz. The δ values of the 4-methoxyphenyl and 4-chlorophenyl groups were found, except where noted, at *ca* 3.8 ppm (MeO) and 6.9 + 7.3 ppm (AA'BB', J *ca* 9; 4xArH) and *ca* 7.1 + 7.4 ppm (AA'BB', J *ca* 9; 4xArH), respectively; therefore their chemical shifts will be omitted from the individual spectra. Exact molecular mass determinations were made at 70eV with an MS 902 instrument equipped with a direct inlet system.

*(2*RS,*3*RS*)-3-Acetoxy-1-(4-methoxyphenyl)-4-oxoazetidine-2-carbaldehyde* (**9a**)

Acetoxyacetyl chloride (**8a**) (13.7 g, 0.1 mol) in dry DCM (500 cm^3) was added dropwise (*ca* 20 min) to a mixture of *N,N'*-bis(4-methoxyphenyl)ethanediimine[4] (27 g, 0.1 mol), triethylamine (15.4 cm^3, 0.11 mmol) and dry DCM (2500 cm^3) with continuous stirring at -10°C. The mixture was allowed to warm up to room temperature (*ca* 2 h). 1N HCl (3000 cm^3) was added with vigorous stirring. Stirring was continued overnight. The organic phase was separated and washed with water. The solvent was evaporated at reduced pressure to afford the crude title compound (19 g, 72%) as a light brown oil.

0.8 g of this oil was boiled up with dry methanol. A crystalline product [m.p. 135°C; found: $M^{+\cdot}$, 295.1023; $C_{14}H_{17}NO_6$ requires: $M^{+\cdot}$, 295.1056 ν_{max} (KBr) 3350, 1760, 1720, 1260, 1210, 1100, 1070, 830 cm^{-1}] separated on cooling. This was filtered off, washed with diethyl ether and shown by its ^1H NMR spectrum [δ_H ($CDCl_3$), major component: 2.17s (AcO), 2.81d (10.8; OH), 3.42s (OMe, aliphatic), 4.26dd (5.2, 5.5; 4-H), 4.81dd (10.8, 5.5; 4-CH), 6.02d (5.2; 3-H); minor component: 2.18s (AcO), 3.05d (9.5; OH), 3.44s (OMe, aliphatic), 4.40dd (5.3, 3.5; 4-H), 4.76 (9.5, 3.5; 4-CH), 5.90d (5.3; 3-H)] to be a mixture of the two diastereoisomeric hemiacetals of compound **9a**.

The crude oily carbaldehyde was used in the following step without further purification.

*(2*RS,*3*RS*)-3-Acetoxy-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylic acid* (**10a**)

An aqueous solution (500 cm^3) of $KMnO_4$ (18 g, 110 mmol) was poured into an acetone solution (500 cm^3) of crude carbaldehyde **9a** (19 g, 72 mmol). Slight evolution of heat was observed and precipitation of MnO_2 rapidly started. The mixture was stirred overnight. Na_2SO_3 (*ca* 10 g) was added and stirring was continued for 0.5 h. The MnO_2 was filtered off and the acetone component of the filtrate was distilled off at reduced pressure. The remaining aqueous solution was extracted with DCM and treated with charcoal. Acidification (pH 2) with conc. hydrochloric acid resulted in precipitation of the colourless crystals of the title compound [14.7 g, 72%; m.p. 208°C; found: $M^{+\cdot}$, 279.0716; $C_{13}H_{13}NO_6$ requires: $M^{+\cdot}$, 279.0743; ν_{max} (KBr) 3200-2800, 1780/1760, 1740, 1270, 1250, 1220, 1110, 830 cm^{-1}; δ_H 2.12s (AcO), 4.92d (5.5; 2-H), 6.14d (5.5; 3-H)].

*(3*RS,*4*RS*)-3-Acetoxy-4-diazoacetyl-1-(4-methoxyphenyl)azetidin-2-one* (**11a**)

Carboxylic acid **10a** (15.5 g, 55.5 mmole) was refluxed with $SOCl_2$ (100 cm^3) for 2 h. The mixture was evaporated to dryness at reduced pressure. The residue was treated in THF (130 cm^3) with freshly prepared ethereal diazomethane solution (250 cm^3, *ca* 170 mmol) with ice-water cooling. A colourless crystalline substance started to separate within a few min. The mixture was stirred for 1/2 h. The excess diazomethane was destroyed by adding acetic acid and the crystalline title compound [11.8 g, 70%; m.p. 133°C; found: $M^{+\cdot}$, 303.0858; $C_{14}H_{13}N_3O_5$ requires: $M^{+\cdot}$, 303.0855; ν_{max} (KBr) 2140, 1760, 1630, 1260, 1230, 1110, 830 cm^{-1}; δ_H ($CDCl_3$) 2.14s (AcO), 4.75d (5.4; 4-H), 5.52s (CHN_2), 6.06 (5.4; 3-H)] was filtered off and washed with diethyl ether.

Evaporation to dryness of the combined filtrate and washings and trituration of the residue with diethyl ether afforded a less pure second fraction (3.9 g, 23%; m.p. 125°C) which was shown by TLC (DCM - acetone, 10:0.1) to consist mainly of compound **11a** contaminated with the methyl ester [m.p. 111°C; found: $M^{+\cdot}$, 293.0893; $C_{14}H_{15}NO_6$ requires: $M^{+\cdot}$, 293.0899; ν_{max} (KBr) 1760, 1750, 1260, 1220, 1200, 1100, 830 cm^{-1}; δ_H ($CDCl_3$) 2.13s (AcO), 3.79s + 3.80s (aromatic and ester MeO), 4.84d (5.3; 2-H), 6.12d (5.3; 3-H)] of carboxylic acid **10a** which was isolated in pure form by TLC.

*(3*RS,*4*RS*)-3-(4-Chlorophenoxy)-4-diazoacetyl-1-(4-methoxyphenyl)azetidin-2-one* (**11b**)

Carboxylic acid **10b**[5] (m.p. 186°C; prepared by $KMnO_4$ oxidation of carbaldehyde **9b**; 15 g, 43 mmole) was converted with $SOCl_2$ into the acyl chloride as described above for the preparation of the chloride of carboxylic acid **10a**. When triturated with diethyl ether the dry residue of the mixture turned crystalline. The crystals were filtered off and converted into the crude title compound as described above for the preparation of compound **11a**. The crude product was purified by c.c. (DCM) to afford the pure title compound [63%; m.p. 162°C; found: C, 57.9; H, 3.9; Cl, 9.6; $C_{18}H_{14}ClN_3O_4$ requires: C, 58.15; H, 3.8; Cl, 9.6%; ν_{max} (KBr) 2115, 1740, 1640, 820 cm^{-1}; δ_H (80 MHz; $CDCl_3$) 4.75d (5.5; 4-H), 5.45d (5.5; 3-H), 5.55s ($COCHN_2$)].

*(3*RS,*4*RS*)-3-Acetoxy-4-chloroacetyl-1-(4-methoxyphenyl)azetidin-2-one* (**12a**)

HCl (*ca* 20 mmol) in diethyl ether (10 cm^3) was added dropwise to a vigorously stirred solution of compound **11a** (4.0 g, 12.8 mmol) in dry DCM (80 cm^3) at 0°C. When evolution of nitrogen had ceased, the solution was evaporated to dryness to afford the title compound [4.0 g, 100%; m.p. 141°C; found: $M^{+\cdot}$,

311.0575; $C_{14}H_{14}ClNO_5$ requires: $M^{+\cdot}$, 311.0561; ν_{max} (KBr) 1760sh, 1730, 1240, 1210, 830 cm^{-1}; δ_H ($CDCl_3$) 2.14s (AcO); 4.16 + 4.32 (AB, 15.6; $COCH_2Cl$), 5.18d (5.4; 4-H), 6.15d (5.4, 3-H)] which was allowed to react with KSCN in the following step without any purification.

*(3*RS,*4*RS*)-4-(Chloroacetyl)-3-(4-chlorophenoxy)-1-(4-methoxyphenyl)azetidin-2-one* (**12b**)

The title compound [3.0 g, 97%; m.p. 160°C; found: $M^{+\cdot}$, 379.0464; $C_{18}H_{15}Cl_2NO_4$ requires: $M^{+\cdot}$, 379.0378; ν_{max} (KBr) 1760, 1740, 830, 820 cm^{-1}; δ_H ($CDCl_3$) 4.23 + 4.41 (AB, 16.0; $COCH_2Cl$), 5.26d (5.5; 4-H), 5.54d (5.5; 3-H)] was obtained from diazo compound **11b** (3.0 g, 8.8 mmol) similarly as described for the preparation of compound **12a** from compound **11a**.

*(3*RS,*4*RS*)-3-Acetoxy-1-(4-methoxyphenyl)-3-(thiocyanatoacetyl)azetidin-2-one* (**13a**)

A mixture of chloroacetyl derivative **12a** (3.5 g, 11.2 mmol), dry DMF (120 cm^3), KSCN (3.8 g, 39 mmol) and anhydrous KI (*ca* 0.1 g) was heated for 15 min at 80°C. The solvent was distilled off at *ca* 250 Pa and the residue was triturated with water. The solid product was recrystallized from methanol to afford the title compound [3.65 g, 97%; m.p. 144°C; found: $M^{+\cdot}$, 334.0619; $C_{15}H_{14}N_2O_5S$ requires: $M^{+\cdot}$, 334.0623; ν_{max} (KBr) 2170, 1760, 1740, 1260, 1220, 1100, 830 cm^{-1}; δ_H ($CDCl_3$) 2.17s (AcO), 3.91 + 4.25 (AB, 17.2; $COCH_2SCN$), 5.01d (5.5; 4-H), 6.12d (5.5; 3-H)].

*(3*RS,*4*RS*)-3-(4-Chlorophenoxy)-1-(4-methoxyphenyl)-4-(thiocyanatoacetyl)azetidin-2-one* (**13b**)

The title compound [2.4 g, 76%; m.p. 190°C; found: Cl, 8.8; S, 7.75; $C_{19}H_{15}ClN_2O_4S$ requires: Cl, 8.8; S, 7.95%; ν_{max} (KBr) 2160, 1770, 1730, 830, 820 cm^{-1}; δ_H (DMSO-d_6) 4.34 + 4.64 (AB, 17.3; $COCH_4SCN$), 5.56d (5.6; 4-H), 5.95d (5.6; 3-H)] was obtained from compound **12b** (3.0 g, 7.9 mmol) as described for the preparation of compound **13a** from compound **12a**.

*(3*RS,*4*RS*)-3-Acetoxy-4-(carbamoylthioacetyl)-1-(4-methoxyphenyl)azetidin-2-one* (**14a**), *(4*RS*)-* and *(4*SR*)-4-[(2*RS,*3*SR*)-3-acetoxy-1-(4-methoxyphenyl)-4-oxoazetidin-2-yl]-4-hydroxythiazolidinones* (**15a**)

Finely pulverized compound **13a** (3.0 g, 9 mmol) was added in small portions to a precooled mixture of conc. H_2SO_4 (40 cm^3) and water (4 cm^3) at -2°C. The resulting solution was stirred for 15 min and poured onto ice (*ca* 150 g). The colourless solid material was filtered off and thoroughly washed with water until neutral. The product [10 g, 31%; m.p. 211°C; found: $M^{+\cdot}$, 352.0719; $C_{15}H_{16}N_2O_6S$ requires: $M^{+\cdot}$, 352.0729; the relative abundance of the molecular peak was very low (<2%) because elimination of water to afford

compound **16a** ($M^{+\cdot}$, 334) took rapidly place in the mass spectometer; ν_{max} (KBr) 3500-3150b with several local maxima, 1770, 1740, 1680, 1250, 1215, 1100, 830 cm^{-1}] was shown by TLC (DCM - acetone, 5:1) to be a mixture of *three* compounds (R_f 0.5, *ca* 0.3 and *ca* 0.3) which were tentatively assigned, in this order, the open-chain structure **14a** and the two diastereoisomeric ring tautomeric structures **15a**. When subjected to flash chromatography (DCM - acetone, 20:1 → 5:1) the least polar component (R_f 0.5) disappeared completely. Similarly, in the NMR spectra of the original three component mixture only *two* compounds, *viz.* the two ring tautomers **15a** (ratio 4:1) were seen [δ_H*, major component: 2.19s (AcO), 3.12 + 3.89 (AB, 11.8; 5-H_2), 4.73d (5.3; 2'-H), 6.11d (5.3; 3'-H), 6.70s (OH), 7.81s (NH), 6.85 + 7.60 (AA'BB', 4xArH); minor component: 2.18s (AcO), 3.32 + 3.73 (AB, 12.3; 5-H_2), 4.74d (5.3; 2'-H), 6.11d (5.3; 3'-H), 6.47s (OH), 8.15s (NH), 6.85 + 7.52 (AA'BB', 4xArH); δ_C*, major component: 19.95 + 168.83 (AcO), 37.18 (C-5), 55.10 (MeO), 62.22 (C-2'), 72.23 (C-3'), 87.40 (C-4), 113.70 (C-3" + C-5"), 120.47 (C-2" + C-6"), 129.63 (C-1"), 156.62 (C-4"), 162.96 (C-4'), 172.83 (C-2); minor component: 20.49 + 168.87 (AcO), 36.66 (C-5), 55.07 (MeO), 61.60 (C-2'), 72.22 (C-3'), 87.62 (C-4), 113.70 (C-3" + C-5"), 120.47 (C-2" + C-6"), 129.27 (C-1"), 156.62 (C-4"), 163.10 (C-4'), 172.04 (C-2)].

*(3*RS,*4*RS*)-4-(Carbamoylthioacetyl)-3-(4-chlorophenoxy)-1-(4-methoxyphenyl)azetidin-2-one* (**14b**)

The light yellow title compound [1.7 g; 96%; m.p. 154°C; found: $M^{+\cdot}$, 420.0535; Cl, 8.2; $C_{18}H_{17}ClN_2O_5S$ requires: $M^{+\cdot}$, 420.0547; Cl, 8.4%; the relative abundance of the molecular peak was, as in the **a** series, very low; in contrast to the **a** series and in agreement with the dissimilar tautomeric structures of the two corresponding products, the M-H_2O (*m/z* 402) peak was also of low abundance; instead, an abundant M-HNCO (*m/z* 377; 50%) peak was present in the mass spectrum of compound **14b** whose analogue (*m/z* 309) in the mass spectrum of the epimeric mixture **15a** was much less abundant; ν_{max} (KBr) 3450, 3350, 1770, 1750, 1720, 1690, 840, 830 cm^{-1}; δ_H (DMSO-d_6) 3.68 + 4.07 (AB, 16.5; $COCH_2S$), 5.56d (5.7; 4-H), 5.92d (5.7; 3-H), 7.20 + 7.41 (AA'BB'; ClC_6H_4O), 7.67 + 7.93 (2xbr; $CONH_2$)] was obtained from compound **13b** as described above for the preparation of a mixture of compounds **14a** and **15a**.

*4-[(2*RS,*3*RS*)-3-Acetoxy-1-(4-methoxyphenyl)-4-oxoazetidin-2-yl]thiazol-2(3*H*)-one* (**16a**)

A mixture of the three ring-chain tautomers **14a** and **15a** (two diastereoisomers) (0.5 g, 1.4 mmol) in acetic acid (20 cm^3) was refluxed for 3 h. The solution was evaporated to dryness and the residue was recrystallized from acetic acid to afford the title compound [0.46 g, 98%; m.p. 213°C; found: $M^{+\cdot}$, 334.0647;

* Unprimed locants refer to the thiazole ring, primed locants to the azetidine ring and doubly primed locants to the PMP group

$C_{15}H_{14}N_2O_5S$ requires: $M^{+\cdot}$, 334.0623; ν_{max} (KBr) 3250, 1770, 1740, 1680, 1260, 1220, 1100, 820 cm^{-1}, δ_H* ($CDCl_3$) 2.06s (AcO), 5.11d (4.6; 2'-H), 5.88d (4.6; 3'-H), 6.17s (5-H), 9.52br s (NH)].

*4-[(2*RS,*3*RS*)-3-(4-Chlorophenoxy)-1-(4-methoxyphenyl)-4-oxoazetidin-2-yl]thiazol-2(3*H*)-one* (**16b**)

The title compound [1.5 g, 93%; m.p. 248°C; found: $M^{+\cdot}$, 402.0429; $C_{19}H_{15}ClN_2O_4S$ requires: $M^{+\cdot}$, 402.0441; ν_{max} (KBr) 1750, 1705, 1670, 825, 820 cm^{-1}; δ_H*(DMSO-d_6) 5.39d (4.6; 2'-H), 5.81d (4.6; 3'-H), 6.41s (5-H), 11.55br s (NH)] was obtained from open chain tautomer **14b** (1.7 g; 4.4 mmol) as described above for the preparation of compound **16a** from a mixture of ring-chain tautomers **14a** and **15a**. Compound **16b**, when recrystallized from acetic acid, afforded a product from which the residual solvent could be removed only after prolonged drying for a week over NaOH at *ca* 110°C, 2.5 kPa, followed by a second recrystallization from acetonitrile.

No change took place when a mixture of compound **16b** (0.3 g), methanol (10 cm^3) and Na_2CO_3 (80 mg) in water (2 cm^3) was stirred for 1 h at room temperature.

*4-[(2*RS, *3*RS*)-3-Hydroxy-1-(4-methoxyphenyl)-4-oxoazetidin-2-yl]thiazol-2(3*H*)-one* (**1b**)

A mixture of acetoxy compound (**16a**) (0.33 g, 1 mmol), methanol (15 cm^3) and 1N hydrochloric acid (1.1 cm^3) was refluxed for 10 h and evaporated to dryness. The residue was triturated with DCM and the resulting crystalline product was recrystallized from acetic acid to afford the title compound [0.2 g; 68%; m.p. 173-175°C; found: $M^{+\cdot}$, 292.0523; $C_{13}H_{12}N_2O_4S$ requires: $M^{+\cdot}$, 292.0518; ν_{max} (KBr) 3450, 3250, 1730, 1670 cm^{-1}; δ_H* 4.88d (4.6; 2'-H), 5.12br dd (4.6, 7.5; 3'-H), 5.96br d (7.5; OH), 6.28s (5-H), 10.64br s (NH)].

*(5*RS*)-5-Hydroxy-7-(4-methoxyphenyl)-1,5-dihydrothiazolo[3,4-*a*]pyrazine-3,6(7*H*)-dione* (**7b**)

(*a*) A mixture of compound **1b** (0.11 g, 0.38 mmol), methanol (5 cm^3) and Na_2CO_3 (40 mg, 0.37 mmol) in water (1.5 cm^3) was stirred for 1/2 h at room temperature and evaporated to dryness. The residue was taken up in DCM and purified by TLC (DCM-acetone, 5:1) to afford an amorphous product (0.06 g, 55%), identical (IR, TLC) with the product obtained as described in (**b**).

(*b*) A mixture of acetoxy compound **16a** (0.33 g, 1 mmol), methanol (15 cm^3) and Na_2CO_3 (0.11 g, 1 mmol) in water (5 cm^3) was stirred for 1/2 h at room temperature; during this period a clear solution was formed from the initial suspension. The methanol component of the mixture was distilled off and the remaining

* Primed numbers refer to the azetidine, unprimed to the thiazole ring

aqueous solution was extracted with DCM. The combined DCM solutions were dried ($MgSO_4$) and evaporated to dryness. The residue (0.24 g) was purified by TLC (DCM-acetone, 5:1) to afford the amorphous title compound [0.19 g, 65%; m.p. 75-76°C; found: $M^{+\cdot}$, 292.0544; $C_{13}H_{12}N_2O_4S$ requires: $M^{+\cdot}$, 292.0518; ν_{max} (KBr) 3350br, 1680 cm^{-1} (doublet); δ_H ($CDCl_3$) 4.04 + 4.25 (2xdd, 14.0, 1.5 and 2.5, respectively; 1-H_2), 4.73br s (OH), 5.86dd (1.5 and 2.5; 8-H), 6.05s (5-H)].

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