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On the Anomalous Behaviour of Certain 1-(4-Methoxyphenyl)azetidin-2--ones towards Cerium(IV) Ammonium Nitrate (CAN). Structure-Reactivity Studies†‡

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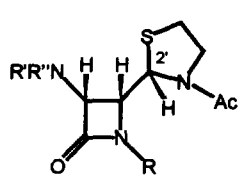
Abstract: On treatment with CAN, acetylthiazolidinylazetidin-2-one **12** undergoes ring transformation to afford compound **22**, similarly to azetidin-2-ones **2a** and **2b** studied earlier (all with like configurations at C-4 and C-2'). In contrast, acetylthiazolidinylazetidin-2-one **11** is *N*-demethoxyphenylated under the same conditions, similarly to azetidin-2-ones **1a** and **1b** studied earlier (all with unlike configurations at C-4 and C-2'). Both epimers, with like as well as unlike configurations at C-4 and C-2', of acetyloxazolidinyl derivative **7** are *N*-demethoxyphenylated by CAN. These observations support the mechanism, suggested earlier for the CAN induced novel ring transformation reaction.

Recently the 2'-epimers of (3*RS*,4*RS*)-4-(3-acetylthiazolidin-2-yl)-1-(4-methoxyphenyl)-3-(subst. amino)azetidin-2-ones were found to react differently with cerium(IV) ammonium nitrate (CAN):[2] while the (3*RS*,4*RS*,2'*SR*) isomers **1a** and **1b** were, in agreement with the usual behaviour of 1-(4-methoxyphenyl)azetidin-2-ones,[3] readily de(4-methoxyphenylated) to the corresponding compounds **3a** and **3b**, their 2'-epimers **2a** and **2b** underwent, on treatment with CAN under the same conditions, a novel ring transformation reaction to afford compounds **4a** and **4b**, respectively.[2] The divergent behaviour of the

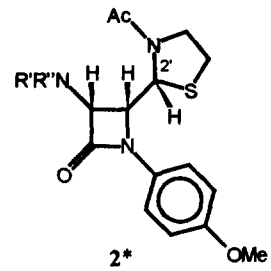
† Simple and Condensed β-Lactams, Part 25. For Part 24, see ref. 1

‡ Dedicated to Professor Hans Suschitzky on the occasion of his 80th birthday on December 14th 1995



1:* R= 4-MeOC$_6$H$_4$

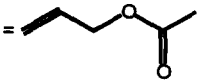
3:* R= H



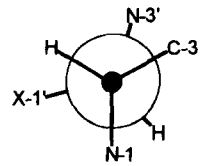
2*

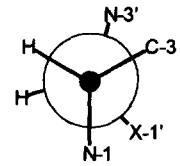
4*

1-4, **a**: R'R"N = phthalimido

b: R' =  , R" = H

2'-epimers was shown to be the consequence of restricted rotation about the pivot bond linking the two heterocycles and of the widely differing spatial structures of the conformers of the epimers. The partial structures of the epimers around the pivot bond, as derived from MM calculations,[2] are shown in Figure 1a.





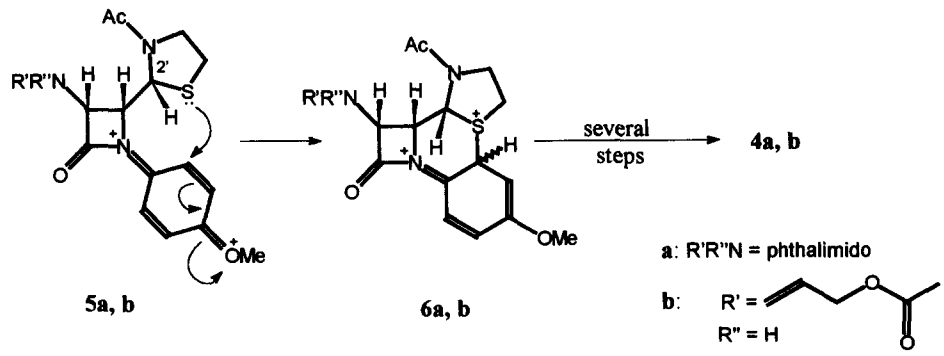
	(3*S*,4*S*,2'*R*)		(3*S*,4*S*,2'*S*)	
	a	*b*	*a*	*b*
∢ H-C(4)-C(2')-H	177°	178.7°	29°	27.6°
$J_{4\text{-H},2\text{'-H}}$ calculated	10.7 Hz	9.8 Hz	7.6 Hz	6.9 Hz
$J_{4\text{-H},2\text{'-H}}$ observed	10.0 Hz	8.3 Hz	7.2 Hz	4.2 Hz

Figure 1. Newman projections around the C-4 – C-2' bond, H–C(4)–C(2')–H dihedral angles and $J_{4\text{-H},2\text{'-H}}$ coupling constants (*a*) in the (3*S*,4*S*,2'*R*) and (3*S*,4*S*,2'*S*) enantiomers of thiazolidine derivatives **1a** and **2a** (X=S) and (*b*) in the (3*S*,4*S*,2'*R*) and (3*S*,4*S*,2'*S*) enantiomers of the two epimeric compounds **7** (X=O)

The nucleophilic thiazolidine sulfur atom is seen to be in the vicinity of the doubly positively charged and highly electrophilic iminium moiety in intermediates **5**[4] formed on CAN treatment of compounds **2a** and **2b**,

* All compounds discussed in this paper are racemic; only one enantiomer is shown.

and should, therefore, be able to attack the latter; as a result, compounds **6a** and **6b**, respectively, will be formed which then react further to afford ultimately ring transformation products **4a** and **4b**. On the other



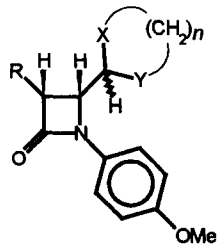
5a, b **6a, b**

hand, the thiazolidine sulfur atom and the quinone imine moiety are far away from each other in the 2'-epimeric intermediates resulting on CAN treatment of compounds **1a** and **1b**. Therefore no interaction between them is possible and normal demethoxyphenylation takes place.[2]

Here we report our attempts to extend the scope of the novel ring transformation reaction. To this end, a series of compounds containing various saturated heterocyclic groups — differing from those present in compounds **1** and **2** either in the nature of their heteroatoms (compounds **7**, **9**, **10**) or their ring size (compound **8**) — attached to position 4 of the β-lactam ring, as well as *p*-chlorophenoxy analogue **11** and 3,4-*trans* compound **12** were prepared and their reactions with CAN were studied.

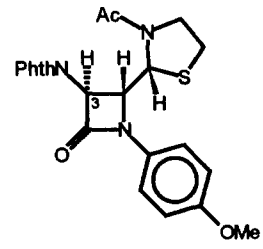
Preparation of compounds **7-12**

The common starting substance for the preparation of compounds **7-10** was the known aldehyde **13**[5]. Its condensation with 2-aminoethanol and 3-mercaptoprop-1-ylamine afforded compounds **14** and **15**, respectively, the latter as an inseparable 1:1 mixture of its 2'-epimers. Subsequent acetylation of compound **14**



7-11

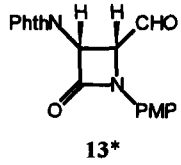
	R*	X	Y	*n*
7	PhthN	AcN	O	2
8	PhthN	AcN	S	3
9	PhthN	O	S	2
10	PhthN	S	S	2
11	4-ClC_6H_4O	AcN	S	2



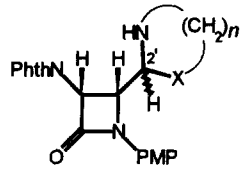
12

* PhthN = phthalimido

led to the formation of compound **7**, as an inseparable 3:2 mixture of its 2'-epimers, while similar treatment of compound **15** gave compound **8** as a single epimer. Since the latter was obtained in 98% yield starting with the 1:1 mixture of the epimers of compound **15**, epimerization must have taken place, in the course of acetylation (obviously *via* ring-chain tautomerization of the 1,3-thiazane moiety of compound **15**).



13*



14*, **15***

	X	*n*
14	O	2
15	S	3

MM calculations similar to those[2] carried out for the epimeric compounds **1a** and **2a** have shown (*i*) that rotation about the pivot bond linking the two heterocycles in both epimers of compound **7** is also highly restricted, (*ii*) that the spatial structures of the most stable conformers of these epimers are practically identical with those of the corresponding epimeric thiazolidine derivatives **1a** and **2a** and (*iii*) that in the oxazolidine compounds **7**, too, the dihedral H–C(4)–C(2')–H angle and the corresponding vicinal coupling constants are larger for the epimer with unlike configurations at C-4 and C-2' than for the epimer with like configurations at these centers. Although the agreement between the calculated and observed coupling constants of the oxazolidine derivatives is less satisfactory than in their thiazolidine analogues, we believe that the more abundant epimer of compound **7** ($J_{4\text{-H},2'\text{-H}}$ 4.2) is the (3*RS*,4*RS*,2'*RS*) epimer while the less abundant epimer ($J_{4\text{-H},2'\text{-H}}$ 8.3) possesses the (3*RS*,4*RS*,2'*SR*) configuration.

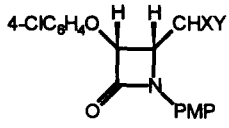
On the other hand, the observed $J_{4\text{-H},2'\text{-H}}$ coupling constant (10.6) of the single epimer of compound **8** obtained was very similar to that of compound **1a** (10.0); therefore we believe that this epimer of compound **8** is the (3*RS*,4*RS*,2'*SR*) compound.

Condensation of aldehyde **13** with 2-mercaptoethanol and ethane-1,2-dithiol afforded compounds **9** and **10**, respectively, the former as a 4:1 mixture of its 2'-epimers.

The synthesis of compound **11** was based on cycloaddition of 1,2-bis[*N*-(4-methoxyphenyl)imino]ethane[6,7] [whose synthesis was considerably improved by carrying out the condensation of the dihydrate of glyoxal trimer with *p*-anisidine in water] and the ketene generated *in situ* from (4-chlorophenyl)acetyl chloride.[8] In addition to the main product, the desired imine **16**, minor amounts of a dimeric product (**19**) were also formed. Treatment with hydrochloric acid of the product mixture brought about hydrolysis of the imine to aldehyde **17**. When the crude mixture of the latter and dimer **19** was boiled up with

* PhthN = phthalimido, PMP = 4-methoxyphenyl troughout this paper

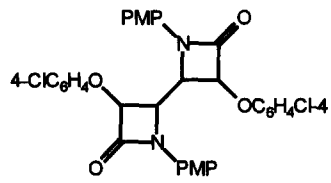
methanol, the aldehyde was converted into its hemiacetal **18** as a mixture of two epimers, which could easily be separated from the insoluble dimer. Formation of dimers closely related to compound **19** in ketene imine cycloadditions has been observed before by Alcaide *et al.*[5b] Without characterization of compound **19** it is, therefore, assumed simply by analogy[5b] that the stereochemistry of both lactam rings is 3,4-*cis*. Whether dimer **19** is racemic or a *meso* compound, remains, however, unknown.



16: X+Y= N-PMP

17: X+Y= O

18: X= OMe, Y= OH



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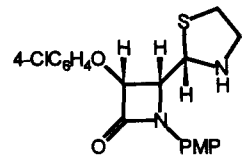


20

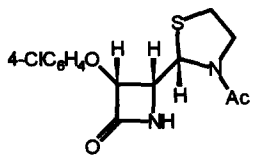
Condensation of hemiacetal **18** with 2-aminoethanethiol afforded compound **20**, as shown by its ^{1}H NMR spectrum and in contrast to all similar cases studied by us so far, as a single, *viz.* the (3*RS*,4*RS*,2'*SR*) epimer. Acetylation then furnished the (3*RS*,4*RS*,2'*SR*) epimer of compound **11**.

Compound **12** was obtained in quantitative yield by treatment of compound **2a** with DBU in dichloromethane.

Reaction of compounds **7-12** *with CAN*

Compounds **8-10** were found to be highly sensitive to CAN and to afford intractable multicomponent mixtures of decomposition products on treatment with this reagent.

In contrast, from the mixtures obtained on treatment with CAN of the remaining compounds, defined products were isolated. From the two acetylthiazolidinyl derivatives **11** and **12** the former was simply demethoxyphenylated, while the latter underwent ring transformation to afford compounds **21** and **22**,



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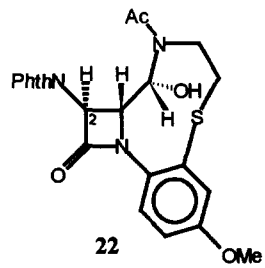

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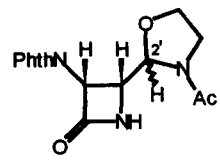

23

respectively, the latter being the 2-epimer of compound **4a**, similarly as compound **12** is the 3-epimer of compound **2a**.

The 3:2 mixture of the 2'-epimers of compound **7**, when treated with CAN, afforded a 3:2 mixture of the 2'-epimeric demethoxyphenylation products **23**, the relative configurations of the more and less abundant epimers of the demethoxyphenylation product being identical with those of the more and less abundant epimers, respectively, of compound **7**. Thus *both epimers* of compound **7** are independently demethoxyphenylated by CAN.

The divergent behaviour of the two acetylthiazolidinyl derivatives **11** and **12** parallels the divergent behaviour of the 2'-epimeric pairs of compounds **1a** and **2a**, and **1b** and **2b** on treatment with CAN and supports our view[2] concerning the decisive role of the relative configuration of C-4 and C-2' in determining the mode of reaction of all these compounds with CAN. While compounds **1a** and **1b** as well as compound **11** with unlike configurations at C-4 and C-2' are demethoxyphenylated on treatment with CAN, compounds **2a** and **2b** as well as compound **12** with like configurations at C-4 and C-2' undergo ring transformation under the same conditions. Comparison of the behaviour of the 3-epimeric compounds **12** and **1a** furthermore demonstrates that the configuration at C-3 has no effect on the mode of reaction with CAN.

The identical behaviour of the two 2'-epimers of compound **7** (demethoxyphenylation in both cases) indicates that the condition of like configurations at C-4 and C-2' is only a necessary but not a sufficient condition for ring transformation to take place on treatment with CAN. Examination of the transformation of intermediates **5a** and **5b** into intermediates **6a** and **6b**, respectively, clearly shows that a further prerequisite for ring transformation is the presence of a sufficiently strong *C*-nucleophile in sterically favourable position relative to the doubly positively charged quinone imine moiety of intermediates similar to **5a** and **5b**. By replacing the thiazolidine sulfur by an oxazolidine oxygen atom which is a considerably weaker *C*-nucleophile, intramolecular nucleophilic attack at the quinone imine moiety is prevented even if the oxazolidine oxygen atom (in one of the 2'-epimers of compound **7**) is in favourable steric position for such an attack to take place. Therefore both 2'-epimers are demethoxyphenylated.

EXPERIMENTAL

Evaporations to dryness were carried out at reduced pressures (*ca* 2.5 kPa). $MgSO_4$ was invariably used as the drying agent. Column chromatographic (c.c.) separations of product mixtures were carried out using Kieselgel G 60 (Merck) as the adsorbent with pressure differences of *ca* 100 kPa between the upper and lower ends of the columns; eluents are indicated in parentheses. For preparative t.l.c. separations 20x20 cm glass plates coated with Kieselgel 60 $PF_{254+366}$ (Merck; thickness of adsorbent layer *ca* 1.5 mm) were used; solvents are indicated in parentheses, ethylacetate was used as the eluent. The purity of the products was checked by t.l.c. on DC-Alufolien 60 PF_{254} (Merck); the individual compounds were detected by UV irradiation or by using 5% ethanolic molybdo-phosphoric acid as the reagent.

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 NMR spectra were obtained with a Varian XL-400 spectrometer in $CDCl_3$ + DMSO-d_6 solutions (unless otherwise stated) and using tetramethylsilane as the internal reference. Selected δ values will only be given; coupling constants (in parantheses) are in Hz.

Molecular mechanics calculations: optimalization of the geometry of one enantiomer of both epimers of oxazolidinyl derivative **7** was carried out as before[2] using the block diagonal method in the MMX(87) force field.[9] The coupling constants $J_{4\text{-H},2'\text{-H}}$ for the epimers in their most stable calculated conformations were obtained by application of the modified Karplus equation.[10]

*(3*RS*,4*RS*)-4-[(2*RS*)- and (2*SR*)-3-acetyloxazolidin-2-yl]-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2--one* (**7**), *mixture of epimers*

Aldehyde **13**[5] (0.7 g, 2 mmol) was dissolved in toluene (40 cm^3) with gentle heating (*ca* 45°C) and freshly distilled 2-aminoethanol (0.15 g, 2.2 mmol) in dichloromethane (10 cm^3) was dropwise added with continuous stirring within 10 min. The mixture was refluxed for 2 h in a flask equipped with a Dean-Stark separator and evaporated to dryness. The residue, crude compound **14**, was taken up in dichloromethane (20 cm^3), the solution was washed with water and dried. Acetic anhydride (1 cm^3, 10 mmol) was added. The mixture was kept for 2 days at room temperature and evaporated to dryness. The residue was triturated with methanol to afford a 3:2 mixture (NMR) of the (*3RS,4RS,2'RS*) and the (*3RS,4RS,2'SR*) epimers of the title compound [0.68 g, 78%; m.p. 234°C; found: C, 63.2; H, 4.9; N, 9.8; $C_{23}H_{21}N_3O_6$ (435.4) requires: C, 63.45; H, 4.85; N, 9.65%; ν_{max} (KBr) 1780, 1750, 1720, 1710 cm^{-1}; δ_H,* (*3RS,4RS,2'RS*) epimer: 1.89s (Ac), 3.15m + 3.55m (4'-H_2), 3.79s (OMe), 3.86m + 4.03m (5'-H_2), 4.92dd (5.5, 4.2; 4-H), 5.46d (5.5; 3-H), 5.49d (4.2; 2'-H); (*3RS,4RS,2'SR*) epimer: 1.74 br s (Ac), 3.43m + 3.75m (4'-H_2), 3.77s (OMe), 3.9-4.1m (5'-H_2), 4.71dd (5.5, 8.3; 4-H), 5.59d (5.5; 3-H), 5.70 br d (8.3; 2'-H)] which was filtered off and washed with diethyl ether.

*(3*RS*,4*RS*)-1-(4-Methoxyphenyl)-4-[(2*RS*)- and (2*SR*)-1,3-thiazan-2-yl]-3-phthalimidoazetidin-2-one* (**15**), *mixture of epimers*

A mixture of 3-mercaptopropylammonium chloride[11] (3.7 g, 29 mmol) [obtained from 1,3-thiazane-2--thione[12]], NaOAc·3 H_2O (4.75 g, 35 mmol) in water (30 cm^3) was added to aldehyde **13**[5] (7.8 g, 22.3 mmol) in dioxan (70 cm^3) with continuous stirring at room temperature. Stirring was continued for 1 h while the initial

* Primed locants refer to the oxazolidine ring

clear solution gradually turned into a thick white paste. The crystalline product was filtered off and thorougly washed with water to afford a 1:1 mixture (NMR) of the 2'-epimers of the title compound [8.26 g, 87%; m.p. 208°C (from dioxan - water); found: N, 9.65; S, 7.65; $C_{22}H_{21}N_3O_4S$ (423.5) requires: N, 9.9; S, 7.55%; ν_{max} (KBr) 3400, 1790, 1760, 1720 cm^{-1}; δ_H* 1.35-1.63m (5'-H_2), 2.26m + 2.6-2.95m + 3.12m (4'-H_2 + 6'-H_2), 2.80 br (NH), 3.80s (OMe), 4.47dd (5.0, 9.6; 4-H, epimer *A*), 4.49 br d (9.4; 2'-H, epimer B), 4.52 br d (9.6; 2'-H, epimer A), 4.54dd (5.3, 9.4; 4-H, epimer *B*), 5.54d (5.3; 3-H, epimer *B*), 5.57 d (5.0; 3-H, epimer *A*).

(3RS,4RS)-4-[(2SR)-3-Acetyl-1,3-thiazan-2-yl]-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2-one (**8**)

Acetic anhydride (2.1 cm^3, 21.2 mmol) was added to a solution of the mixture of epimers of compound **15** (3.0 g, 7.1 mmol) in dichloromethane (40 cm^3). The mixture was kept for 3 days at room temperature to afford the title compound [3.2 g, 98%; m.p. 262-264°C (from dichloromethane); found: N, 9.0; $C_{24}H_{23}N_3O_5S$ (465.5) requires: N, 9.05%; ν_{max} (KBr) 1785, 1750, 1720, 1650 cm^{-1}; δ_H* 1.53s (Ac), 1.60m + 1.86m (5'-H_2), 2.50m + 3.32m (6'-H_2), 3.48m + 3.61m (4'-H_2), 3.67s (OMe), 5.45d (4.7; 3-H), 5.50 br d (10.6; 2'-H), 5.54dd (4.7, 10.6; 4-H)] as a single epimer which was filtered off and washed with diethyl ether.

(3RS,4RS)-1-(4-Methoxyphenyl)-4-[(2RS)- and (2SR)-1,3-oxathiolan-2-yl]-3-phthalimidoazetidin-2-one (**9**), *mixture of epimers*

Aldehyde **13**[5] (2.1 g, 6 mmol) was dissolved in toluene (90 cm^3) with gentle heating (*ca* 45°C). 2-Mercaptoethanol (0.7 cm^3, 10 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added and the mixture was refluxed for 2 h in a flask equipped with a Dean-Stark separator while a crystalline product gradually separated. The mixture was allowed to cool and the product was filtered off and washed successively with methanol and diethyl ether to afford the title compound [1.9 g, 87%; m.p. 205-208°C (from toluene); found: N, 6.7; $C_{21}H_{18}N_2O_5S$ (410.4) requires: N, 6.85%; ν_{max} (KBr) 1790, 1760, 1720 cm^{-1}; δ_H ($CDCl_3$)†, more abundant epimer: 2.94dd (7.0, 4.5; S-CH_2), 3.54dt (9.2, 7.0) + 4.12dt (9.2, 4.5; O-CH_2), 3.82s (OMe), 4.59dd (5.2, 8.4; 4-H), 5.36d (8.4; 2'-H), 5.60d (5.2; 3-H); less abundant epimer: 2.90m (S-CH_2), 3.72m + 4.40m (O-CH_2), 4.58dd (5.7, 8.6; 4-H), 5.38d (8.6; 2'-H), 5.61d (5.7; 3-H)] as a 4:1 mixture (NMR) of its 2'-epimers.

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* Primed locants refer to the thiazane ring

† Primed locants refer to the oxathiolane ring

(3RS,4RS)-4-(1,3-Dithiolan-2-yl)-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2-one (**10**)

This compound [m.p. 269°C (from toluene); found: N, 6.55; S, 15.2; $C_{21}H_{18}N_2O_4S_2$ (426.5) requires: N, 6.55; S, 15.05%; ν_{max} (KBr) 1790, 1760, 1720 cm^{-1}; δ_H ($CDCl_3$)* 2.95-3.25m (4'-H_2 + 5'-H_2), 3.82s (OMe), 4.61dd (5.2; 10.2; 4-H), 4.80d (10.2; 2'-H), 5.57d (5.2; 3-H)] was similarly obtained in 82% yield starting with aldehyde **13**[5] (5.7 mmol) and ethane-1,2-dithiol (6.6 mmol).

1,2-Bis[N-(4-methoxyphenyl)imino]ethane

A hot mixture of *p*-anisidine (123.2 g, 1 mol), methanol (400 cm^3) and water (500 cm^3) was dropwise added to a hot aqueous (1000 cm^3) solution of glyoxal trimer dihydrate (33.75 g, 0.16 mol). A thick paste of the yellow crystalline title compound gradually formed. The product [125 g (93%), m.p. 162°C (from methanol - water), lit. 159°C[6] and 153-154°C[7]] was filtered off and washed successively with cold methanol and a large amount of diethyl ether.

(3RS,4RS)-3-(4-Chlorophenoxy)-4-[(hydroxy)(methoxy)methyl]-1-(4-methoxyphenyl)azetidin-2-one (**18**), *mixture of 1'- epimers*

(4-Chlorophenoxy)acetyl chloride (21.1 g, 103 mmol) in freshly distilled dichloromethane (560 cm^3) was added within *ca* 1.5 h dropwise to a mixture of ethane-1,2-bis(4-methoxyphenylimine) (30.2 g, 113 mmol), triethylamine (15.4 cm^3, 110 mmol) and dichloromethane (1100 cm^3) with continuous stirring at 0°C. Stirring was continued for 1.5 h with the cooling bath removed while the mixture warmed up to room temperature. 1N HCl (1300 cm^3) was added and stirring was continued for another 1.5 h while imine **16** was converted into aldehyde **17**. The two phases were separated. The organic phase was washed with water, dried and evaporated to dryness. The residue (a mixture of aldehyde **17** and dimer **19**) was boiled up with methanol (220 cm^3) and the insoluble dimer was filtered off while the mixture was still hot. The filtrate was cooled to 0°C, the crystalline hemiacetal **18** was filtered off and washed with ice-cold methanol. A second fraction [total yield 18.0 g, 49%; m.p. 110°C; found: Cl, 9.85; N, 3.9; $C_{18}H_{18}ClNO_5$ (363.5) requires: Cl, 9.75; N, 3.85%; ν_{max} (KBr) 1750 cm^{-1}; δ_H ($CDCl_3$), major epimer 3.30d (9.4; OH), 3.44s (CH-O*Me*), 3.80s (Ar-O*Me*), 4.38dd (4.2, 5.0; 4-H), 5.05dd (4.2, 9.4; 4-CH), 5.33d (5.0, 3-H); minor epimer 2.89d (8.5, OH), 3.39s (CH-O*Me*), 3.79s (Ar-O*Me*), 4.45dd (3.5, 5.5; 4-H), 4.96dd (3.5, 8.5; 4-CH), 5.28d (5.5; 3-H); ratio of epimers 6:4 (NMR)] was obtained by concentrating the combined filtrate and washings of the first to *ca* 1/2 its original volume and isolating the resulting crystalline product.

* Primed locants refer to the dithiolane ring

(3RS,4RS)-3-(4-Chlorophenoxy)-1-(4-methoxyphenyl)-4-[(2SR)-thiazolidin-2-yl]azetidin-2-one (**20**)

A solution of 2-mercaptoethylammonium chloride (0.75 g, 6.6 mmol) and NaOAc·3 H_2O (1.2 g, 8.8 mmol) in water (8.8 cm^3) was added to mixture **18** of epimeric hemiacetals (2.0 g, 5.5 mmol) in dioxan (8 cm^3). The resulting suspension was stirred for 2 h at room temperature while first a clear solution and subsequently a new suspension was formed. The insoluble product was filtered off and thoroughly washed with water and then with a small amount of cold methanol to afford the title compound [2.12 g, 98%; m.p. 182-184°C (from dioxan - water); found: Cl, 9.25; N, 7.05; S, 8.5; $C_{19}H_{19}ClN_2O_3S$ (390.9) requires: Cl, 9.05; N, 7.15; S, 8.2%; ν_{max} (KBr) 3330, 1740 cm^{-1}; δ_H ($CDCl_3$)* 2.18 br (NH), 2.73 + 2.98 (2xddd, 9.8, 6.0, 9.0 and 9.8, 2.8, 5.8, respectively; 5'-H_2), 3.13 + 3.54 (2xbr m; 4'-H_2), 3.80s (OMe), 4.46dd (9.1, 5.4; 4-H), 5.02 br m (2'-H), 5.24 d (5.4; 3-H).

*(3RS,4RS)-4-[(2SR)-3-Acetylthiazolidin-2-yl]-3-(4-chlorophenoxy)-1-(4-methoxyphenyl)azetidin-2-one [(3RS,4RS,2'SR)-***11***]*

A mixture of compound **20** (2.12 g, 5.4 mmol), dry dioxan (20 cm^3), acetic anhydride (1.6 cm^3, 16 mmol) and a catalytic amount of DMAP was refluxed for 1.5 h while the initial suspension turned into a clear solution. On cooling, part of the colourless crystalline title compound separated. This was filtered off and washed with diethyl ether. The combined filtrate and washings were evaporated to dryness and the viscous oily residue was triturated with diethyl ether to afford a second crystalline fraction of the title compound [total yield 2.1 g, 89%; m.p. 210°C (from dioxan); found: Cl, 8.5; N, 6.45; $C_{21}H_{21}ClN_2O_4S$ (432.9) requires: Cl, 8.2; N, 6.45%; ν_{max} (KBr) 1750/1730d, 1660 cm^{-1}; δ_H ($CDCl_3$; two rotamers, due to restricted rotation about the N-acetyl bond)* 1.84s + 1.76s (*N*-Ac), 2.92m + 3.05m, 2.96m + 3.19m (5'-H_2), 3.31m + 4.94m, 3.57m + 3.93m (4'-H_2), 3,78s (OMe), 4.62dd (9.9, 5.3) + 4.78dd (8.1, 4.7; 4-H), 5.30d (5.3) + 5.26d (4.7; 3-H), 5.50d (9.9) + 6.15d (8.1; 2'-H)] which was filtered off and washed with diethyl ether.

(3RS,4SR)-4-[(2SR)-3-Acetylthiazolidin-2-yl]-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2-one (**12**)

A mixture of compound **2a**[2] (2.25 g, 5 mmol), freshly distilled dichloromethane (140 cm^3) and DBU (0.15 g, 1 mmol) was allowed to stand for 3 days at room temperature. Acetic acid (1 cm^3) was added and the solution was extracted with water, dried and evaporated to dryness to afford the crystalline title compound [2.20 g, 98%; m.p. 119°C (from dichloromethane); found: S, 7.2; $C_{23}H_{21}N_3O_5S$ (451.5) requires: S, 7.1%;

* Primed locants refer to the thiazolidine ring

ν_{max} (KBr) 1790sh, 1750, 1720, 1650 cm^{-1}; δ_H ($CDCl_3$ + C_6D_6)* 1.73s (Ac), 2.38m + 2.72m (5'-H_2), 2.79m + 3.07m (4'-H_2), 3.53s (OMe), 5.30dd (2.0, 2.5; 4-H), 5.32d (2.5; 3-H), 5.75d (2.0; 2'-H)].

Reactions with CAN

(*a*) An aqueous solution (24 cm^3) of CAN (4.6 g, 8.4 mmol) was dropwise added within 10 min to epimeric mixture **7** (1.3 g, 3 mmol) in acetonitrile (60 cm^3) with continuous stirring at -10°C. Stirring was continued for 10 min at -5°C. The mixture was allowed to warm up to room temperature and extracted with ethyl acetate. The combined organic phases were successively washed with saturated aqueous Na_2CO_3, 10% aqueous $NaHSO_3$ and brine, dried and evaporated to dryness to afford a 3:2 crystalline mixture of *(3*RS,*4*RS*)-4-[(2'*RS*)- and (2'*SR*)-3-acetyloxazolidin-2-yl]-3-phthalimidoazetidin-2-one* [(3*RS*,4*RS*,2'*RS*)- and (3*RS*,4*RS*,2'*SR*)-**23**] [0.63 g, 66%; m.p. 257-259°C (from methanol - diethyl ether); found: C, 58.2; H, 4.55; N, 12.8; $C_{16}H_{15}N_3O_5$ (329.4) requires: C, 58.35; H, 4.6; N, 12.75%; ν_{max} (KBr) 1780, 1760, 1720, 1670 cm^{-1}; δ_H (24°C),† (3*RS*,4*RS*,2'*RS*) epimer: 1.89s (Ac), 3.63m (4'-H_2), 3.99m + 4.14m (5'-H_2), 4.07dd (5.0, 6.8; 4-H), 5.26dd (5.0, 1.4; 3-H), 5.47d (6.8; 2'-H), 8.57 br s (NH); (3*RS*,4*RS*,2'*SR*) epimer (two rotamers, due to restricted rotation about the N-acetyl bond): 2.05s + 2.19s (Ac), 3.2-4.05m (4'-H_2 + 5'-H_2), 3.85dd + ~3.98dd (5.2, 7.8; 4-H), 5.38d + 5.40d (5.2; 3-H), 5.46d + ~5.47d (7.8; 2'-H), 8.0 + 8.76 (2xbr s; NH)] which was triturated with methanol, filtered off and washed with diethyl ether.

(*b*) Compound (3*RS*,4*RS*,2'*SR*)-**11** (0.6 g, 1.4 mmol) was similarly treated with CAN (6.7 mmol). The dry residue (0.39 g), obtained on evaporation to dryness of the combined organic phases, was taken up in a mixture of dichloromethane and methanol, Kieselgel G 60 (1.6 g) was added and the mixture evaporated to dryness. The residue was transferred to a column of Kieselgel G 60 (10 g) and worked up by c.c. (dichloromethane - acetone, 3:1). The combined dry residues of the fractions containing the demethoxyphenylated product were recrystallized from ethyl acetate - acetonitrile to afford *(3*RS,*4*RS*)-4-[(2*SR*)-3-acetylthiazolidin-2-yl]-3-(4-chlorophenoxy)azetidin-2-one* (**21**) [0.20 g, 44%; m.p. 207°C; found: Cl, 10.8; N, 8.5; $C_{14}H_{15}ClN_2O_3S$ (326.8) requires: Cl, 10.85; N, 8.55%; ν_{max} (KBr) 3180, 3100 br, 1750, 1630 cm^{-1}; δ_H* (two rotamers, due to restricted rotation about the N-acetyl bond) 2.15s + 2.25s (Ac), 2.85-3.3m + 3.61m + 4.08m + 4.72m (4'-H_2 + 5'-H_2), 3.97dd (9.6, 4.8) + 4.06dd (9.5, 5.0; 4-H), 4.24dd (4.8, 1.5) + 5.28dd (5.0, 1.8; 3-H), 5.82d (9.6) + 5.29d (9.5; 2'-H), 8.45br + 8.98br (NH).

* Primed locants refer to the thiazolidine ring
† Primed locants refer to the oxazolidine ring

(*c*) Compound **12** (0.26 g, 0.58 mmol) was treated with CAN (1.45 mmol) as described in (*a*) and the mixture was worked up as described in (*b*) (dichloromethane - acetone, 10:2) to afford *(2RS,2aSR,3SR)-4--acetyl-3-hydroxy-9-methoxy-2-phthalimido-2,2a,3,4,5,6-hexahydro-1H-azeto[2,1-f][1,4,7]benzothiadiazon-in-1-one* (**22**) [0.12 g, 44%; m.p. 195°C (from dichloromethane - acetone); ν_{max} (KBr) 3450br, 1790, 1770, 1710, 1650 cm^{-1}; δ_H 1.72s (Ac), 2.76m + 3.43m (6-H_2), 3.50m + 3.89m (5-H_2), 3.79s (OMe), 5.22d (9.3; 3-H), 5.44d (2.5; 2-H), 5.77dd (9.3, 2.5; 2a-H), 6.85dd (8.8, 3.0; 10-H), 7.09d (3.0; 8-H), 7.50d (8.8; 11-H).

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