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On the Anomalous Behaviour of (3*RS*,4*RS*)-[(2*RS*)-3-Acetylthiazolidin-2-yl]-1-(4-methoxyphenyl)azetidin-2-ones towards Cerium(IV) Ammonium Nitrate (CAN). An Unprecedented Oxidative Ring Transformation. †

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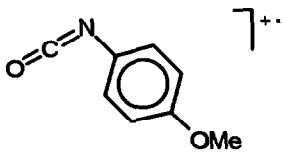
Abstract: Starting with (2*RS*,3*RS*)-1-(4-methoxyphenyl)-4-oxo-3-phthalimidoazetidine-2-carbaldehyde (**1**) the two diastereoisomeric 4-(3-acetylthiazolidin-2-yl)-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2-ones **4a** and **5a** were prepared and converted into their 3-allyloxycarbonylamino analogues **4c** and **5c**, respectively. While the (3*RS*,4*RS*,2'*SR*) isomers **4a** and **4c** were readily *N*-deprotected with cerium (IV) ammonium nitrate (CAN) to yield the expected **6a** and **6c**, respectively, treatment of the (3*RS*,4*RS*,2'*RS*) isomers **5a** and **5c** with CAN led to compounds **7a** and **7c**, respectively, *via* oxidative ring transformation. The structure of compound **7a** was established by an X-ray diffraction study. A rationale, based on AM1 and MMX calculations is given for the dissimilar behaviour of the diastereoisomers.

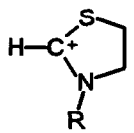
† Simple and Condensed ß-Lactams, Part 18. For Part 17, see ref. 1

N-Deprotection of 1-(4-methoxyphenyl)azetidin-2-ones by treatment with cerium(IV) ammonium nitrate (CAN) is an established method in ß-lactam chemistry.[2] Here we describe the synthesis and anomalous behaviour of two ß-lactams (**5a**, **5c**) which, on treatment with CAN, undergo oxidative ring transformation rather than the expected *N*-deprotection.

Treatment of (2*RS*,3*RS*)-1-(4-methoxyphenyl)-4-oxo-3-phthalimidoazetidine-2-carbaldehyde (**1**)[3] with 2-mercaptoethylammonium chloride and sodium acetate in refluxing aqueous dioxan furnished a mixture of (3*RS*,4*RS*)-4-[(2*SR*)-thiazolidin-2-yl]-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2-one (**2**) and its 2'-epimer (**3**). Subsequent treatment of the crude mixture with acetic anhydride in the presence of 4-dimethylaminopyridine (DMAP) in refluxing dioxan gave a mixture of the corresponding acetyl derivatives **4a** and **5a** which were separated by fractional crystallization to yield the less and more polar isomers **4a** and **5a** in 49 and 31% yield, respectively, from compound **1**.*† Treatment with CAN of the (3*RS*,4*RS*,2'*SR*) isomer **4a** under the usual conditions afforded, as expected, the deprotected product **6a** in 64% yield. However, 2'-epimer **5a** afforded, under the same conditions, an anomalous product containing, as revealed by exact mass spectrometric mass determination, one oxygen atom per molecule more than those of the starting compound **5a**. The mass spectrum of the product indicated furthermore that both the 4-methoxyphenyl and the 3-acetylthiazolidin-2-yl groups of the starting **5a** had been affected in the course of the reaction. The characteristic fragment ions *m/z* 149 (**a**), 130 (**b**) and 88 (**c**) of compound **5a** were namely missing from the mass spectrum of the product. Further structural information came from the ^{1}H n.m.r. spectrum which



a



b : R = Ac
c : R = H

revealed that the 4-methoxyphenyl group of **5a** had been replaced by a trisubstituted phenyl group in the product, with the newly introduced third substituent being attached to one of the *meta* positions relative to the methoxy group. Structure **7a** was finally established for the product by an X-ray diffraction study (see below).

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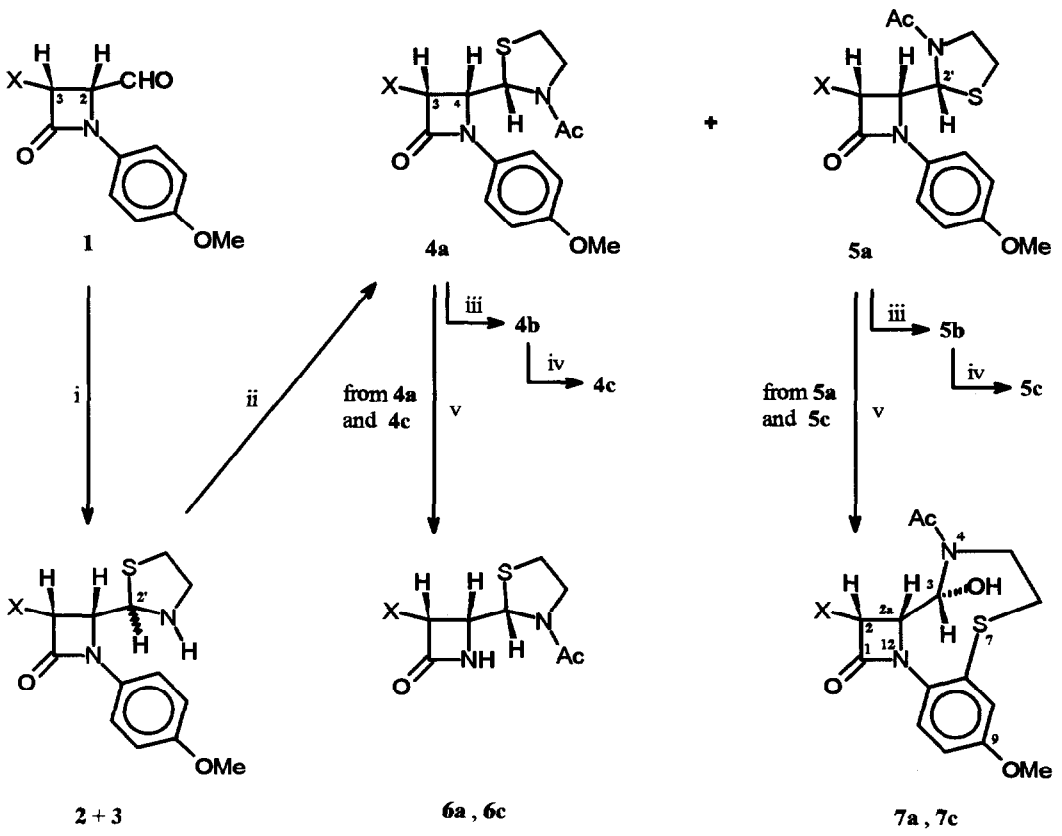
* Compounds **4a** and **5a** could be separated also by chromatography (Kieselgel; benzene - ethyl acetate, then acetone, finally methanol) but considerable decomposition took thereby place.

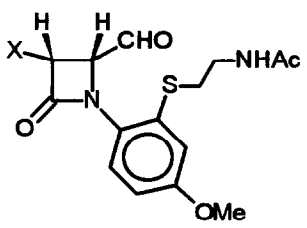
† For the assignment of relative configurations to the epimers, see below.



Scheme 1. Only one enantiomer is shown. **1-4**, **4a**, **5a**, **6a**, **7a**: X = phthalimido; **4b**, **5b**: X = amino; **4c**, **5c**, **6c**, **7c**: X = allyloxycarbonylamino. i: H_3N^+-CH_2-CH_2-SH Cl^-, NaOAc, aq. dioxan, reflux; ii: Ac_2O, DMAP, dioxan, reflux, then fractional crystallization; iii: $MeNHNH_2$, CH_2Cl_2, r.t.; iv: CH_2=CH-CH_2-O-CO-Cl, pyridine, CH_2Cl_2, 0 °C; v: CAN, MeCN - H_2O, -10 °C

Compound **7a**, when refluxed with methanol, afforded the open-chain isomer (tautomer?) **8a**. The stabilities of the two isomers are apparently such as to permit both of them to exist separately. The EI mass spectra of the isomers, however, were found to be identical. The ^1H and ^{13}C NMR spectra of the isomers, on the other hand, differed considerably, those of isomer **8a** showing the presence of a formyl group attached to the ß-lactam ring and of a -CH_2CH_2NHAc group (with vicinal coupling between the NH and the neighbouring CH_2 protons), in other words rupture of the thiazolidine ring between C-2 and the two hetero atoms. A consideration of these structural features as well as of the presence of a sulfur atom and (similarly to the case of isomer **7a**) of a trisubstituted phenyl ring permitted to derive structure **8a** for the isomer.

Compound **5a**, when treated with CAN in a mixture of acetonitrile and *methanol* (rather than, as usual, in aqueous acetonitrile) yielded the *O*-methyl derivative **9a** of compound **7a**. The relative configurations of C-3 in **9a** and **7a** are shown by the closely similar values of $J_{2a\text{-}H,3\text{-}H}$ to be the same. The same product **9a** was obtained by successive treatment of compound **7a** with thionyl chloride and methanol. The overall retention accompanying this two-step transformation **7a** → **9a** might, in principle, be the result of both steps taking place either with inversion or with retention. However, since back-side attack of nucleophiles at C-3 of compound **7a** and of the corresponding chloride appears to be difficult (see Fig.2), we believe that actually



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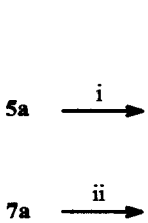
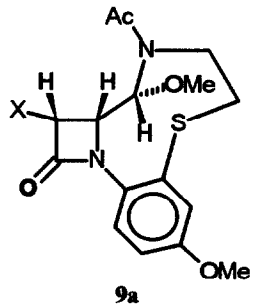
a: X = phthalimido
c: X = allyloxycarbonylamino





9a

X = phthalimido

[i: CAN, MeCN-MeOH, r.t.
ii: $SOCl_2$, 0 °C; then MeOH, r.t.]

both steps take place with retention, replacement of the hydroxy group by chlorine being an S_Ni and replacement of chlorine by the methoxy group being an S_N1 type process taking place *via* cation **14**, similarly to the formation of compounds **7a** and **7c** (Scheme 3).

Dephthaloylation of compounds **4a** and **5a** with methylhydrazine afforded the parent 3-amino compounds **4b** and **5b**, respectively, which were converted into the 3-allyloxycarbonylamino derivatives **4c** and **5c**. The behaviour of the latter towards CAN was found to be analogous to that of the 3-phthalimido derivatives **4a** and **5a**, respectively. Thus, while **4c** was deprotected by CAN to furnish compound **6c** in a normal way, treatment of compound **5c** with CAN afforded compound **7c** *via* oxidative ring transformation. Structure **7c** has been assigned to the product partly by analogy and, more important, on the basis of (i) the observed NOE between 3-H and the acetylmethyl group, (ii) the observed vicinal coupling of 3-H with an exchangeable hydrogen atom (that of the OH group), (iii) the NOEs between one 6-H and 8-H, and 8-H and the aromatic *O*-Me group in the ^1H n.m.r. spectrum, (iv) the absence of fragment ions **a-c** from the mass spectrum and (v) the general similarity of the ^1H n.m.r. and mass spectra of the product in question and of compound **7a**. When kept in methanolic solution for a prolonged period at room temperature, **7c** was, similarly to compound **7a**, converted into the open-chain isomer **8c**. Again, the EI mass spectra of isomers **7c** and **8c** were found to be identical. However, the thermally considerably less demanding FAB spectra were different (*e.g.* only the spectrum of isomer **7c** exhibits an abundant M-18 peak); therefore on the basis of their FAB spectra the isomers are readily distinguished. The ^1H and ^{13}C spectra of the isomers also differed considerably, those of isomer **8c** permitting to establish the presence of the same structural features as in the case of analogue **8a** (see above) and thence of structure **8c**.

X-RAY MOLECULAR STRUCTURE DETERMINATION OF COMPOUND 7a

Single crystals were obtained by recrystallization from DMF-ether. They were found to contain one molecule of DMF per molecule of **7a**. Figure 1 shows the computer drawing of the molecule with thermal ellipsoids and the crystallographic numbering.

Final atomic fractional co-ordinates, together with their e.s.d.s. and equivalent isotropic displacements are given in Table 1. Bond lengths and bond angles are shown in Tables 2 and 3, respectively. As revealed by Figure 1, compound **7a** is the (2*RS*,2a*RS*,3*RS*) isomer. The same configuration may be assigned to compound **7c** by analogy.

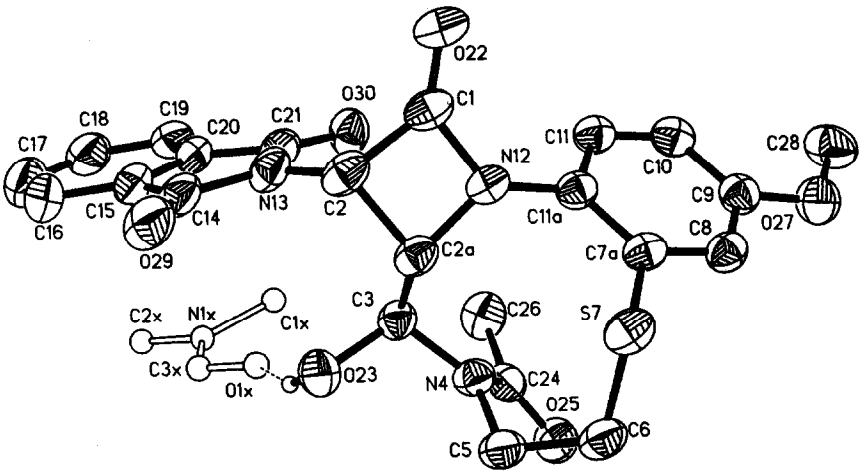


Figure 1. Perspective view of molecule (2*S*,2a*S*,3*S*)-**7a** and the hydrogen bonded solvent DMF with the crystallographic numbering scheme. Thermal ellipsoids are shown at the 40% probability level.

Relative configurations of C-4 and C-2' in compounds 4 (a-c) and 5 (a-c)* and the mechanism of transformations 5a → 7a and 5c → 7c

Comparison of the structures of compounds **5** and **7** reveals that, in the course of the oxidative ring transformation, the sulfur atom does somehow react with the substituent attached to the lactam nitrogen atom, which leads to the formation of a nine-membered ring with concomitant opening of the thiazolidine cycle. The following questions do arise in this connection:

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* The 3,4-*cis* or (3*RS*,4*RS*) configuration of the starting carbaldehyde **1** is, as expected and shown by the values of the $J_{3\text{-H},4\text{-H}}$ coupling constants (4-5 Hz), preserved throughout all reactions leading ultimately to compounds **4c** and **5c**. Therefore only the configuration of C-2' relative to that of C-4 had to be established in compounds **4** and **5**.

Table 1. Atomic coordinates (x10^4) and equivalent isotropic displacement coefficients (x10^3 Å^2), compound **7a**

	x	y	z	U(eq)		x	y	z	U(eq)
C1	8767(3)	11157(3)	325(1)	59(1)	O1x	10315(3)	14709(3)	2095(1)	99(1)
C2	9819(2)	11028(3)	812(1)	60(1)	N1x	10912(3)	16981(3)	2070(1)	88(1)
C2a	8811(2)	10936(3)	1161(1)	52(1)	C1x	9820(6)	17336(7)	1689(3)	185(4)
C3	8782(2)	12132(3)	1563(1)	51(1)	C2x	11756(9)	18082(7)	2224(3)	232(5)
N4	7660(2)	12132(2)	1778(1)	51(1)	C3x	11050(3)	15679(4)	2231(1)	80(1)
C5	7452(2)	10911(3)	2122(1)	63(1)					
C6	6315(3)	10044(3)	1898(1)	64(1)	H2	10239	10133	808	
S7	6320(1)	9148(1)	1262(1)	62(1)	H2a	8790	10010	1326	
C7a	5826(2)	10540(2)	785(1)	50(1)	H3	8860	13035	1390	
C8	4602(2)	10837(3)	651(1)	56(1)	H5	7378	11272	2471	
C9	4161(2)	11882(3)	267(1)	55(1)	H5b	8144	10286	2170	
C10	4977(3)	12643(3)	21(1)	59(1)	H6a	5627	10675	1850	
C11	6201(2)	12347(3)	156(1)	55(1)	H6b	6201	9337	2160	
C11a	6645(2)	11293(2)	534(1)	50(1)	H8	4047	10321	828	
N12	7917(2)	11052(2)	651(1)	53(1)	H10	4692	13376	-239	
N13	10652(2)	12215(2)	897(1)	60(1)	H11	6759	12876	-15	
C14	11846(2)	12099(3)	1188(1)	68(1)	H16	14122	13468	1613	
C15	12365(2)	13555(4)	1194(1)	68(1)	H17	14511	15898	1511	
C16	13507(3)	14086(5)	1418(1)	91(2)	H18	13034	17419	1048	
C17	13727(3)	15518(6)	1357(2)	101(2)	H19	11081	16532	655	
C18	12848(3)	16422(4)	1082(1)	85(1)	H23	10048	12938	2110	
C19	11695(3)	15912(3)	850(1)	70(1)	H26a	6531	15281	1464	
C20	11486(2)	14471(3)	918(1)	60(1)	H26b	7909	14901	1513	
C21	10361(2)	13639(3)	741(1)	55(1)	H26c	6944	14225	1050	
O22	8679(2)	11260(2)	-156(1)	72(1)	H28a	1561	13110	-258	
O23	9806(2)	11924(2)	1978(1)	67(1)	H28b	2740	14035	-98	
C24	6941(2)	13302(3)	1780(1)	54(1)	H28c	2643	12908	-565	
O25	6145(2)	13321(2)	2052(1)	71(1)	H1xa	9326	16492	1619	
C26	7096(3)	14538(3)	1419(1)	72(1)	H1xb	9377	18071	1835	
O27	2936(2)	12042(2)	163(1)	74(1)	H1xc	10030	17668	1357	
C28	2429(3)	13111(4)	-222(1)	86(1)	H2xa	12427	17697	2477	
O29	12291(2)	11000(3)	1385(1)	87(1)	H2xb	12041	18444	1914	
O30	9368(2)	14041(2)	519(1)	65(1)	H2xc	11388	18847	2392	
					H3x	11690	15193	2470	

Equivalent isotropic *U* defined as one third of the trace of the orthogonalized U_{ij} tensor
O1x - C3x and H1xa - H3x are atoms of the solvent (DMF)

Table 2. Bond lengths (Å), compound **7a**

C1-C2	1.541(3)	C11a-N12	1.419(3)
C1-N12	1.375(4)	N13-C14	1.405(3)
C1-O22	1.202(3)	N13-C21	1.406(3)
C2-C2a	1.560(4)	C14-C15	1.475(5)
C2-N13	1.438(3)	C14-O29	1.206(4)
C2a-C3	1.512(3)	C15-C16	1.391(4)
C2a-N12	1.479(3)	C15-C20	1.389(4)
C3-N4	1.460(3)	C16-C17	1.372(7)
C3-O23	1.415(3)	C17-C18	1.382(6)
N4-C5	1.476(3)	C18-C19	1.398(5)
N4-C24	1.357(3)	C19-C20	1.381(4)
C5-C6	1.526(4)	C20-C21	1.477(4)
C6-S7	1.810(3)	C21-O30	1.208(3)
S7-C7a	1.786(2)	C24-O25	1.224(3)
C7a-C8	1.378(3)	C24-C26	1.498(4)
C7a-C11a	1.398(4)	O27-C28	1.432(4)
C8-C9	1.398(3)	O1x-C3x	1.229(4)
C9-C10	1.393(4)	N1x-C1x	1.448(7)
C9-O27	1.357(3)	N1x-C2x	1.401(8)
C10-C11	1.379(4)	N1x-C3x	1.279(4)
C11-C11a	1.396(3)		

C1x - C3x, N1x and O1x are atoms of the solvent (DMF)

Table 3. Bond angles (°), compound **7a**

C2-C1-N12	91.7(2)	C1-N12-C2	95.4(2)
C2-C1-O22	135.8(3)	C1-N12-C11a	130.3(2)
N12-C1-O22	132.5(2)	C2a-N12-C11a	133.1(2)
C1-C2-C2a	85.8(2)	C2-N13-C14	123.2(2)
C1-C2-N13	115.9(2)	C2-N13-C21	125.1(2)
C2a-C2-N13	118.5(2)	C14-N13-C21	111.5(2)
C2-C2a-C3	116.5(2)	N13-C14-C15	105.7(2)
C2-C2a-N12	87.1(2)	N13-C14-O29	124.0(3)
C3-C2a-N12	115.6(2)	C15-C14-O29	130.3(2)
C2a-C3-N4	112.2(2)	C14-C15-C16	131.5(3)
C2a-C3-O23	106.1(2)	C14-C15-C20	108.7(2)
N4-C3-O23	111.1(2)	C16-C15-C20	119.8(3)
C3-N4-C5	117.4(2)	C15-C16-C17	118.2(3)
C3-N4-C24	123.6(2)	C16-C17-C18	121.7(4)
C5-N4-C24	117.4(2)	C17-C18-C19	121.2(4)
N4-C5-C6	113.9(2)	C18-C19-C20	116.4(3)
C5-C6-S7	115.6(2)	C15-C20-C19	122.7(2)
C6-S7-C7a	102.1(1)	C15-C20-C21	108.2(3)
S7-C7a-C8	118.7(2)	C19-C20-C21	129.0(2)

(i) At what stage of the presumably multistep transformation and

(ii) in what manner (among others: before, simultaneously with or after opening of the thiazolidine ring) does the reaction of the sulfur atom with the lactam nitrogen substituent take place?

(iii) Why are the (2*RS*,2a*RS*,3*RS*) diastereoisomers **7** obtained both from **5a** and **5c** as the only or, at least, the main products (isolated yields 90 and 66%, respectively); in other words, why is the oxidative ring transformation diastereoselective?

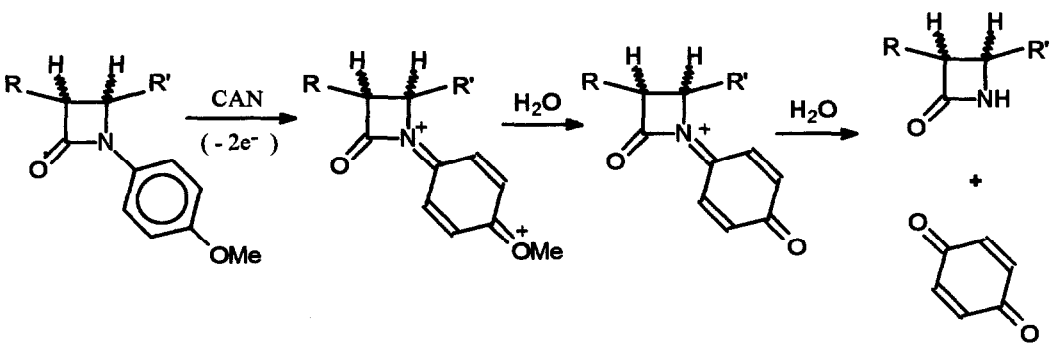
(iv) What are the relative configurations of C-4 and C-2' in diastereoisomers **4a-c** and **5a-c**?

(v) Why does ring transformation take place only with the more polar diastereoisomers **5a** and compound **5c** derived from the former, while epimers **4a** and **4c** are, under the same conditions, simply deprotected; in other words, why is the reaction with CAN diastereospecific?

(vi) What is the stereochemistry of the transformations **5** → **7**? Do they take place with (overall) retention or inversion?

As to the first question, there appears to be now general agreement concerning the mechanism of *N*-de(4-methoxyphenylation) (*i.e.* *N*-deprotection) of ß-lactams by CAN. The reaction is thought to start with loss of two electrons from the *N*-substituent to give first an intermediate quinonoid dication which is then successively *O*-demethylated by water and hydrolyzed (Scheme 2).[4] In our case R' is a (3-acetylthiazolidin-2-yl) group. Although the sulfur atom of the latter could, in principle, interfere with oxidation of the *N*-substitu-

Scheme 2. *N*-De(4-methoxyphenylation) of ß-lactams by CAN



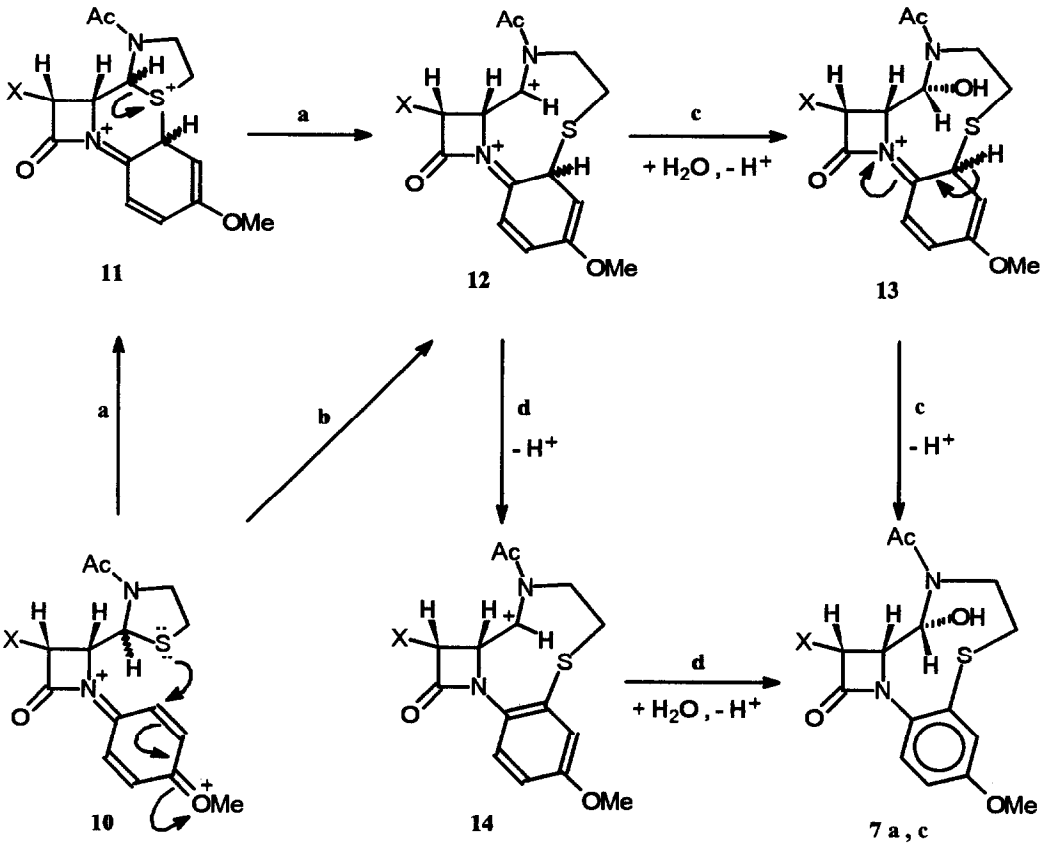
ent,* actually it does not. This is clearly shown by successful *N*-deprotection by CAN of diastereoisomers **4a** and **4c**, as well as by the fact that the oxidation state of the sulfur atom does not change in the course of ring transformation **5** → **7**.

On the other hand, the highly electrophilic quinonoid moieties of compounds **10** which, on the basis of Scheme 2, may be postulated to be the first intermediates formed on treatment with CAN of compounds **4a**,

* Divalent sulfur is known to be oxidized to the sulfoxide by CAN[5]

4c, **5a** and **5c** appear to be ideally suited for intramolecularly reacting with the nucleophilic sulfur atom to yield the tetracyclic dication **11** and thence, by cleavage of the bond which had been originally the C-2 - S bond of the thiazolidine ring, the tricyclic dication **12** (Scheme 3, path *a*). According to this picture attack of the sulfur atom at the *N*-substituent of the lactam ring takes place before opening of the thiazolidine ring. Alternatively, these two events could take place simultaneously (path *b*). The third possibility [*cf.* question (ii), above], *viz.* that opening of the thiazolidine ring takes place prior to formation of the new S-C bond, may, however, definitely be ruled out (see below).

Scheme 3. Possible pathways of formation of compounds **7a** and **7c**

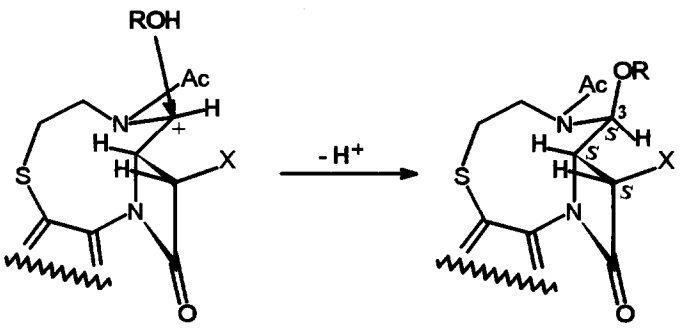


X = Phthalimido and allyloxycarbonylamino, respectively.

Only one enantiomer shown

Subsequently intermediate **12** is converted into the final product in two steps: hydroxylation of the cationic carbon atom and rearomatization of the cyclohexadiene ring by proton loss either in this or the

reversed order (paths *c* and *d*, respectively). In any case, the water molecule should attack the ring system exclusively or, at least, predominantly at the less hindered face, *i.e.* from "outside" (see Fig.2); therefore intermediate **13** as well as products **7a** and **7c** or, at least, their main components should possess the (2*RS*,2a*RS*,3*RS*) configuration which explains the observed stereoselectivity of the reaction [*cf.* question (iii), above].



14a, c **7a, c** (R=H), **9a** (R=Me)
(2*S*,2a*S*,3*S* enantiomers)

Figure 2. Hydroxylation (R=H) and methoxylation (R=Me) of cations **14a** and **c** (**a**: X = phthalimido, **c**: X = allyloxycarbonylamino).

In the course of transformation **5** → **10** → **12** the chiral character of C-2' (numbering of compounds **5** and **10**) is lost. Moreover, at first sight, intermediate **12** should be accessible from both diastereoisomers **4** and **5**. Yet, it is only the (3*RS*,4*RS*,2'*RS*) diastereoisomers **5a** and **c** which undergo ring transformation, while their 2'-epimers **4a** and **c** are simply deprotected to yield the *N*-unsubstituted ß-lactams **6a** and **c**, respectively, deprotection taking place as shown in Scheme 2 with R' = 3-acetylthiazolidin-2-yl.

Thus, the thiazolidine cycle does interfere with the normal course of deprotection only in the (3*RS*,4*RS*,2'*RS*) series and is unable to exert the same effect in the (3*RS*,4*RS*,2'*SR*) series, presumably because interaction of the sulfur atom with the *N*-substituent is not possible in the latter case. In other words, intermediate **12** is assumed to be accessible only in the (3*RS*,4*RS*,2'*RS*) series (*i.e.* from compounds **5a** and **5c**).

In order to rationalize this assumption, it had to be assumed that rotation about the pivot bond linking the hetero rings in compounds **4** and **5** is efficiently hindered and that only compounds **5a** and **5c** are able to adopt a conformation in which the sulfur atom may interact with the lactam nitrogen substituent.

In order to test this hypothesis, molecular mechanics calculations were carried out for one enantiomer, each, of compounds **4a** and **5a**. Optimalization of the geometry using the block diagonal method in the MMX(87) force field[6] has shown that in the most stable conformation of the (3*S*,4*S*,2'*R*) enantiomer of **4a** the sulfur atom and the 4-methoxyphenyl group are far away from each other, while in the most stable

conformation of the (3*S*,4*S*,2'*S*) enantiomer of **5a** they are in each other's vicinity (Figure 3); and furthermore that these conformations are extremely stable, *i.e.* that rotation about the pivot bonds linking the hetero rings is impossible in both cases.

Since these conformations may hardly be assumed to change much following loss of two electrons from the 4-methoxyphenyl group, it follows that intermediates **12** are indeed accessible only from diastereoisomer **5a** (and, by analogy, from **5c**), *i.e.* that only these diastereoisomers should undergo oxidative ring transformation rather than *N*-deprotection on treatment with CAN.

The observation that, in the course of *N*-deprotection of diastereoisomers **4a** and **4c**, the thiazolidine ring is retained suggests that cleavage of the 3-acetylthiazolidine rings of compounds **5a** and **5c** requires, after oxidation of the lactam nitrogen substituent, electrophilic assistance by the quinonoid moieties of the resulting type **10** intermediates (*cf.* Scheme 3), in other words that, in the course of transformation **5** → **10** → **7**, opening of the thiazolidine ring may not precede formation of the new S-C bond [*cf.* question (ii), above].

Since only the more polar diastereoisomer **5a** (and the derived compound **5c**) have been found to undergo oxidative ring transformation, it follows that these compounds, together with compound **5b**, possess the (3*RS*,4*RS*,2'*RS*) configuration while the configurations of the less polar diastereoisomers **4a**, as well as of the derived compounds **4b** and **4c**, are (3*RS*,4*RS*,2'*SR*) [*cf.* questions (iv) and (v), above].

The calculated optimal geometries are supported by the ^{1}H n.m.r. spectra. Application of the modified Karplus equation[7] to compounds **4a** and **5a** in their calculated most stable conformations leads to the values $J_{4\text{-H},2'\text{-H}}$, 10.7 and 7.6 Hz of the vicinal coupling constants for compounds **4a** and **5a**, respectively, which compare well with the measured values of 10.0 and 7.2 Hz, respectively.

From a comparison of the relative configurations of compounds **5a** and **5c** [(3*RS*,4*RS*,2'*RS*)] with those of compounds **7a** and **7c** [(2*RS*,2a*RS*,3*RS*)] it follows that replacement of the C-2' - S bond of compounds **5a** and **5c** by the C-3 - O bond of compounds **7a** and **7c** or, in other words, ring transformation has taken place with overall retention [*cf.* question (vi), above]. This requires temporary transformation of the carbon atom undergoing replacement of its *S*- by an *O*-substituent into a cationic center as shown in Scheme 3; direct, S_N2 type substitution (which would be improbable from the outset) would result in inversion.

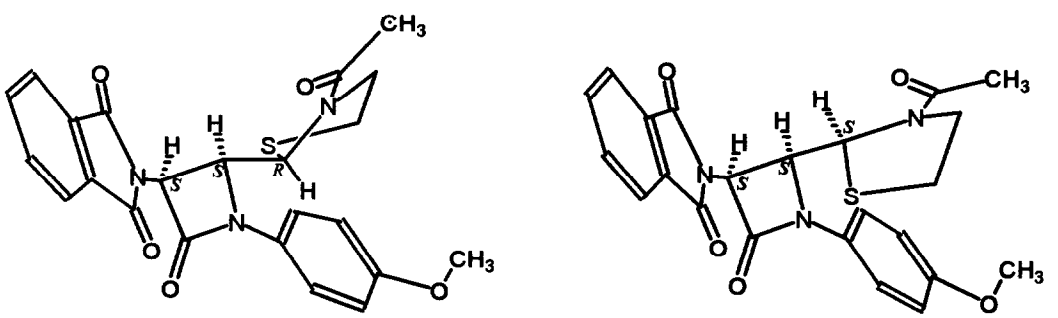
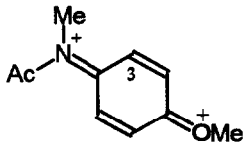
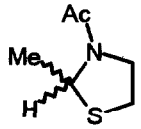


Figure 3. Optimalized geometries of compounds **4a** (left) and **5a** (right)

Finally model AM1-MO calculations[8] were carried out in order to support our assumption concerning intramolecular nucleophilic addition of the thiazolidine sulfur atom to the quinonoid moiety of intermediate **10** (Scheme 3). The intermolecular reaction of quinonoid dication **15** and 3-acetyl-2-methylthiazolidine **16** was selected as the model reaction. The calculated values of the orbital coefficients at C-3 of the LUMO of



15



16

dication **15** and at sulfur of the HOMO of compound **16** were 0.3703 and 0.7908, respectively. These values indicate that both the electrophile and the nucleophile are soft, *i.e.* their reaction is energetically favourable. A similar conclusion is reached on the basis of the calculated energies of the relevant orbitals.[9a] The calculated energies of the LUMO of the electrophile (**15**) and of the HOMO of the nucleophile (**16**) were quite similar (-10.17 and -9.42 eV, respectively). Therefore the perturbation of these orbitals must be decisive. Due to the low value of the $E^{Nu}_{HOMO.} - E^{El}_{LUMO}$ difference the Coulomb term of the Klopman-Salem equation[9b] will be overruled by the orbital term, *i.e.* we have here an orbital controlled reaction.

The present and our earlier observations with 1-(4-methoxyphenyl)-4-(tetrazol-5-ylmethyl)azetidin-2-one,[10] thus, indicate that substituents in position 4 may inhibit *N*-de(4-methoxyphenylation) of ß-lactams.

EXPERIMENTAL

Separations of product mixtures by column chromatography (CC) were carried out at normal or reduced (10-25 kPa) pressure using Kieselgel G 60 (Merck) as the adsorbent. For preparative TLC separations 20 x 20 cm glass plates coated with Kieselgel $PF_{254+366}$ (Merck; thickness of adsorbent layer 1.5 mm) were used. The purity of the products was checked and their R_f values were determined on DC-Alufolien 60 F_{254} (Merck); the individual compounds were detected by UV irradiation or using iodine, 5% ethanolic molybdo-, or tungsto-phosphoric 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. ^1H and ^{13}C NMR spectra were obtained with Varian XL-100 or 400 spectrometers in $CDCl_3$ solutions at ca. 50 °C, unless otherwise stated, and using tetramethylsilane as the internal reference compound; *J* values are given in Hz. EI mass spectra were obtained at 70 eV with an AEI MS 902 instrument equipped with a direct insertion system. Positive ion FAB mass spectra and MIKE spectra were obtained with a VG ZAB-2SEQ spectrometer with reversed geometry and equipped with an LSIMS source and a caesium gun; glycerol (gly) and *m*-nitrobenzyl alcohol (NOBA) were used as the matrix solvents.

*(3*RS,*4*RS*)-4-[(2*SR*)- and (2*RS*)-3-acetylthiazolidin-2-yl]-1-(4-methoxyphenyl)-3-phthalimidoazetidin-2-one* (**4a** *and* **5a**)

An aqueous solution (50 cm^3 of 2-mercaptoethylammonium chloride (7.1 g, 63 mmol) was treated with sodium acetate (5.2 g, 63 mmol) and the mixture was added to the suspension of (*2RS,3RS*)-1-(4-methoxyphenyl)-4-oxo-3-phthalimidoazetidine-2-carbaldehyde (**1**)[3] (17.5 g, 50 mmol) in dioxan 40 cm^3). The mixture was refluxed for 40 min. and evaporated to dryness at reduced pressure. The residue was triturated with water. The crystalline product was filtered off and washed successively with water, methanol and diethyl ether to yield a mixture (18.4 g) of diastereoisomers **2** and **3**.

The mixture was suspended in anhydrous dioxan (320 cm^3). Acetic anhydride (22 cm^3, 0.23 mmol) and DMAP (0.3 g) were added and the mixture refluxed for 4 h. The crystalline product (crude compound **5a**) which separated on cooling was recrystallized from dioxan to give the more polar diastereoisomer **5a** (7.0 g, 31%; m.p. 295-296 °C) in pure form.

The mother liquor of crude **5a** was evaporated to dryness and the residue recrystallized from methylene chloride - hexane to afford the less polar diastereoisomer **4a** (11.0 g, 49%; m.p. 235-241 °C).

Compound **4a**, found C, 60.90; H, 4.60; N, 9.45; S, 7.00;

Compound **5a**, found C, 61.00; H, 4.65; N, 9.45; S, 6.95;

$C_{23}H_{21}N_3O_5S$ (451.50) requires C, 61.2; H, 4.7; N, 9.3; S, 7.1%

Compound **4a**; ν_{max} (KBr) 1770 sh, 1740, 1700, 1630 cm^{-1}; — δ_H 1.85 (s, Ac), 2.82+3.05 (J_{gem}=-10.5, J_{vic}=9.3, 6.8 and 6.5, 2.7, respectively, 5'-H_2), 3.28+4.88 (J_{gem}=-12.1, J_{vic}=9.3, 6.5 and 6.8, 2.7, respectively, 4'-H_2), 3.80 (s, OMe), 4.66 (dd, J=5.6 and 10.0, 4-H), 5.61 (d, J=5.6, 3-H), 5.62 (d, J=10.0, 2'-H), 6.89+7.35 (AA'BB', J=9.0, 4xArH), 7.82+7.94 (m, 4xArH, phthaloyl group).

Compound **5a**: ν_{max} (KBr) 1770 sh, 1730, 1695 cm^{-1}; — δ_H 1.94 (s, Ac), 2.85+2.98 (J_{gem}=-11.0, J_{vic}=6.8, 6.8 and 6.5, 5.1, respectively, 5'-H_2), 3.54+3.88 (J_{gem}=-11.3, J_{vic}=6.8, 6.5 and 6.8, 5.1, respectively, 4'-H_2), 3.82 (s, OMe), 4.75 (dd, J=5.3 and 7.2, 4-H), 5.46 (d, J=5.3, 3-H), 5.77 (d, J=7.2, 2'-H), 6.91+7.39 (AA'BB', J=9.0, 4xArH), 7.75+7.89 (m, 4xArH, phthaloyl group); — EI-MS (200 °C), *m/z* (I%) 451 (48), $M^{+\bullet}$; 409 (3), $[M-42]^{+\bullet}$; 366 (2); 302 (18); 301 (20); 293 (38); 260 (22); 259 (45); 199 (8); 160 (10); 149 (19), **a**; 130 (90), **b**; 88 (130-42) (*100*), **c**; 43 (48), Ac^+.

Dephthaloylation of compounds **4a** *and* **5a**

(*a*) A mixture of compound **4a** (10.9 g, 24 mmol), dry dichloromethane (270 cm^3) and methylhydrazine (1.9 cm^3, 35 mmol) was stirred for 72 h at room temperature. The resulting solution was washed successively with 1N NaOH (25 cm^3) and water (2x25 cm^3), dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The residue was recrystallized from propan-2-ol to give *(3*RS,*4*RS*)-4-[(2*SR*)-3-acetylthiazolidin-2-yl]-3-amino-1-(4-methoxyphenyl)azetidin-2-one* (**4b**) (5.0 g, 65%; m.p. 184 °C).

Found C, 55.80; H, 6.05; N, 12.9; S, 9.75. $C_{15}H_{19}N_3O_3S$ (321.4) requires C, 56.05; H, 5.95; N, 13.05; S, 10.0%. ν_{max} (KBr) 3480, 3420, 1710, 1625 cm^{-1}. — δ_H* 1.68 and 1.89 (br, 3-NH_2), 1.78 and 1.85

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* Two isomers (*ca.* 57:43) in solution, due to restricted rotation about the N-CO bond

(s, Ac), 2.91+3.05 and 3.03+3.14 (J_{gem}=-10.5 and -10.5, J_{vic}=8.9, 7.2 and 7.0, 2.8, and 7.5, 6.5 and 6.5, 4.0, respectively, 5'-H_2), 3.34+4.92 and 3.71+4.00 (J_{gem}=-12.0 and -11.0, J_{vic}=8.9, 7.0 and 7.2, 2.8, and 7.5, 6.5 and 6.5, 4.0, respectively, 4'-H_2), 3.77 (s, OMe), 4.32 (dd, J=5.0 and 10.0) and 4.41-4.66m, (4-H), 4.57 (br d, J=5) and 4.41-4.46m (3-H), 5.35 and 5.97 (d, J=10.0 and 7.2, respectively, 2'-H), 6.84+7.25 and 7.28 (AA'BB', J=9.0, 4xArH).

(*b*) By applying the same procedure to compound **5a** (10.6 g, 23.5 mmol), *(3*RS*,4*RS*)-4-[(2*RS*)-3-acetylthiazolidin-2-yl]-3-amino-2-(4-methoxyphenyl)azetidin-2-one* (**5b**) [6.5 g, 86%; m.p. 131 °C (from propan-2-ol)] was obtained.

Found C, 55.8; H, 5.95; N, 13.0; S, 9.8. $C_{15}H_{19}N_3O_3S$ (321.4) requires C, 56.05; H, 5.95; N, 13.05; S, 10.0%. ν_{max} (KBr) 1705, 1615 cm^{-1}. — δ_H ($CDCl_3$+DMSO-d_6) 1.78 (br s, NH_2), 2.13 (s, Ac), 2.76 (m, 5'-H_2), 3.26+3.57 (J_{gem}=-10.0, J_{vic}=5.5, 4.0 and 8.8, 7.6, respectively, 4'-H_2), 3.79 (s, OMe), 4.47 (br d, J=5.6, 3-H), 5.10 (dd, J=5.6 and 1.7, 4-H), 5.70 (d, J=1.7, 2'-H), 6.85+7.28 (AA'BB', J=9.0, 4xArH).

N-*Allyloxycarbonylation of compounds* **4b** *and* **5b**

(*a*) A solution of allyl chloroformate (2.4 cm^3, 22.5 mmol) in dry dichloromethane (15 cm^3) was added dropwise to a mixture of compound **4b** (5.9 g, 18.3 mmol), dry dichloromethane (180 cm^3) and pyridine (1.85 cm^3, 23 mmol) with ice-water cooling. The mixture was stirred for 1 h, washed with water (2x20 cm^3), dried ($MgSO_4$) and evaporated to dryness at reduced pressure.The residue was triturated with diethyl ether to afford *(3*RS*,4*RS*)-4-[(2*SR*)-3-acetylthiazolidin-2-yl]-3-allyloxycarbonylamino-1-(4-methoxyphenyl)azetidin-2-one* (**4c**) [7.0 g, 94%; m.p. 207 °C (from ethyl acetate - hexane)].

Found C, 56.0; H, 5.7; N, 10.3; S, 7.65. $C_{19}H_{23}N_3O_5S$ (405.45) requires C, 56.3; H, 5.7; N, 10.35; S, 7.9%. ν_{max} (KBr) 1725, 1685, 1610 cm^{-1}. — δ_H* 1.88 (s, Ac), 3.03+3.11 (J_{gem}=-11.0, J_{vic}=7.5, 6.7 and 4.4, 6.5, respectively, 5'-H_2), 3.43+3.90 (J_{gem}=-11.0, J_{vic}=7.5, 6.5 and 4.4, 6.7, respectively, 4'-H_2), 3.78 (s, OMe), 4.57 (dd, J=5.5 and 6.0, 4-H), 4.62 (d, J=5.5, OCH_2), 5.23+5.33 (J_{gem}=-1.3, J_{cis}=10.5, J_{trans}=16.5, CH=CH_2), 5.38 (dd, J=5.5 and 10.0, 3-H), 5.83 (d, J=6.0, 2'-H), 5.92 (ddt, J=16.5, 10.5 and 5.5, C*H*=CH_2), 6.84 (br d, J=10.0, NH), 6.86+7.31 (AA'BB', J=8.8, 4xArH).

(*b*) When the same procedure was applied to compound **5b** (6.5 g, 20.3 mmol), *(3*RS*,4*RS*)-4-[(2*RS*)-3-acetylthiazolidin-2-yl]-3-allyloxycarbonylamino-1-(4-methoxyphenyl)azetidin-2-one* (**5c**) [7.27 g, 88%; m.p. 129 °C (from ethyl acetate - hexane)] was obtained.

Found C, 56.15; H, 5.75; N, 10.25; S, 7.8. $C_{19}H_{23}N_3O_5S$ (405.45) requires C, 56.3; H, 5.7; N, 10.35; S, 7.9%. ν_{max} (KBr) 3340, 1770, 1720, 1660 cm^{-1}. — δ_H 2.10 (s, Ac), 2.81+2.86 (J_{gem}=-11.5, J_{vic}=7.0, 2.5 and 9.5, 7.0, respectively, 5'-H_2), 3.18+3.54 (J_{gem}=-9.5, J_{vic}=7.0, 2.5 and 9.5, 7.0, respectively, 4'-H_2), 3.79 (s, OMe), 4.59+4.63 (*AB*X, J_{gem}=-13, J_{vic}=5.5 and 5.5; OCH_2), 5.25+5.33 (J_{gem}=-1.3, J_{cis}=10.5, J_{trans}=16.8, CH=CH_2), 5.28 (dd, J=5.5 and 1.8, 4-H), 5.37 (dd, J=5.5 and 9.0, 3-H), 5.60 (d, J=1.8, 2'-H), 5.63 (br d, J=9.0, NH), 5.93 (ddt, J=16.8, 10.5 and 5.5, C*H*=CH_2), 6.85+7.29 (AA'BB', J=8.8, 4xArH).

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* Data of the more abundant rotamer

— δ_C* 23.58 ($NCOCH_3$), 30.08 (C-5'), 50.46 (C-4'), 55.45 (OMe), 58.10 (C-4), 58.54 (C-3), 63.78 (C-2'), 66.26 (OCH_2), 114.40 (C-3"+C-5"), 118.15 ($CH=CH_2$), 118.71 (C-2"+C-6"), 130.58 (C-1"), 132.32 ($CH=CH_2$), 155.33 (OCONH), 156.44 (C-4"), 164.45 (C-2), 169.19 ($NCOCH_3$). — EI-MS (200 °C), *m/z* (I%) 405 (18), $M^{+\bullet}$; 347 (13); 274 (20); 265 (21); 198 (8); 149 (20), **a**; 130 (85), **b**; 88 (130-42) (*100*), **c**; 43 (17), Ac^+ ; 41 (16) $[C_3H_5]^+$.

Reaction of compounds **4a**, **4c**, **5a** *and* **5c** *with CAN*

(*a*) An aqueous (80 cm^3) solution of CAN (15 g, 27 mmol) was added within 10 min. dropwise to a solution of compound **4a** (4.5 g, 10 mmol) in acetonitrile (150 cm^3) at -10 °C. The mixture was stirred for 10 min. Ethyl acetate (200 cm^3) was added and the organic phase washed successively with saturated aqueous Na_2CO_3 (50 cm^3), 10% aqueous $NaHSO_3$ (50 cm^3), saturated aqueous Na_2CO_3 (40 cm^3) and brine (20 cm^3), dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The gradually crystallizing residue was taken up in a small amount of methanol and filtered off to give *(3*RS*,4*RS*)-4-[(2*SR*)-3-acetylthiazolidin-2-yl]-3-phthalimidoazetidin-2-one* (**6a**) [2.2 g, 64%; m.p. 275 °C (from acetonitrile)].

Found C, 55.7; H, 4.3; N, 12.2; S, 9.05. $C_{16}H_{15}N_3O_4S$ (345.4) requires C, 55.65; H, 4.4; N, 12.15; S, 9.3%. ν_{max} (KBr) 1760, 1740, 1690 cm^{-1}. — δ_H (two rotamers) 2.16 and 2.36 (s, Ac), 2.79-3.06 (m, 5'-H_2), 3.22m+3.63m+3.93m+4.71m (4'-H_2), 3.95 and 4.15 (dd, J=9.0 and 5.2, and 10.0 and 5.3, respectively, 4-H), 5.48 and 5.53 (d, J=5.2 and 5.3, respectively, 3-H), 5.46 and 5.64 (d, J=10.0 and 9.0, respectively, 2'-H), 6.97 and 7.00 [br s, N(1)-H], 7.75-7.95 (m, 4xArH, phthaloyl group).

(*b*) Similar treatment with CAN of compound **4c** (17.5 mmol) led to a crude product which was purified by CC (dichloromethane - acetone, 2:1) to give *(3*RS*,4*RS*)-4-[(2*SR*)-3-acetylthiazolidin-2-yl]-4-allyloxycarbonylaminoazetidin-2-one* (**6c**) [2.75 g, 52%; m.p. 224 °C (from propan-2-ol)].

Found C, 47.95; H, 5.9; N, 14.1; S, 10.45. $C_{12}H_{17}N_3O_4S$ (299.35) requires C, 48.15; H, 5.7; N, 14.05; S, 10.7%. ν_{max} (KBr) 1750 b, 1670 sh, 1650 cm^{-1}. — δ_H ($CDCl_3$+DMSO-d_6) (two rotamers) 2.17 and 2.25 (s, Ac), 2.82-3.12 (m, 5'-H_2), 3.18m+4.67m and 3.64m+4.02m (4'-H_2), 3.86 and 3.83 (dd, J=10.0 and 5.0, and 9.5 and 4.8, respectively, 4-H), 4.53-4.65 (m, OCH_2), 5.05 and 5.13 (dd, J=9.5 and 5.0, and 9.7 and 4.8, respectively, 3-H), 5.22 and 5.19+5.33 and 5.32, respectively, (J_{gem}=-1.3, J_{cis}=10.5, J_{trans}=17.0, CH=CH_2), 5.41 and 5.80 (d, J=10.0 and 9.5, respectively, 2'-H), 5.86-5.99 (m, C*H*=CH_2), 7.95 and 7.92 (d, J=9.5 and 9.7, respectively, 3-NH), 8.30 and 7.68 [N(1)-H].

(*c*) An aqueous (65 cm^3) solution of CAN (23.1 g, 42.1 mmol) was added as described in (*a*) to a solution of compound **5a** (6.8 g, 15.1 mmol) in acetonitrile (110 cm^3) and the mixture stirred for 10 min. The resulting *(2*RS*,2a*RS*,3*RS*)-4-acetyl-3-hydroxy-9-methoxy-2-phthalimido-2,2a,3,4,5,6-hexahydro-1*H*-azeto-[2,1-f][1,4,7]benzothiadiazonin-1-one* (**7a**) [6.35 g, 90%; m.p. 188 °C (from DMF - water] which gradually crystallized, was filtered off and washed successively with acetonitrile and ethyl acetate.

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* Doubly primed locants refer to the *N*-aryl group

Found C, 56.15; H, 4.6; N, 8.25; S, 6.8. $C_{23}H_{21}N_3O_6S$+1.5 H_2O (494.5) requires C, 55.85; H, 4.9; N, 8.5; S 6.5%. ν_{max} (KBr) 1770/1750 (d), 1690 cm^{-1}. — δ_H ($CDCl_3$+DMSO-d_6) 1.68 (s, Ac), 2.79+3.38 (J_{gem}=-14.7, J_{vic}=2.7, 2.3 and 12.5, 2.9, respectively, 6-H_2), 3.56+3.77 (J_{gem}=-14.4, J_{vic}=12.5, 2.7 and 2.9, 2.3, respectively, 5-H_2), 3.79 (s, OMe), 5.52 (br d, J=9.4, 3-H), 5.66 (d, J=5.3, 2-H), 5.73 (dd, J=5.3 and 9.4, 2a-H), 6.19 (br, 3-OH), 6.90 (dd, J_o=8.8, J_m=2.8, 10-H), 7.04 (d, J_m=2.8, 8-H), 7.77 (d, J_o=8.8, 11-H), 7.85+7.93 (m, 4xArH, phthaloyl group). — δ_C ($CDCl_3$+DMSO-d_6) 21.58 ($NCOCH_3$), 34.07 (C-6), 42.81 (C-5), 55.41 (OMe), 55.83 (C-2), 61.23 (C-2a), 78.24 (C-3), 115.49 (C-10), 122.60 (C-8), 124.26 (C-11), 127.82 (C-7a), 131.64 (C-11a), 157.27 (C-9), 162.84 (C-1), 170.67 ($NCOCH_3$), 123.49d+123.64d+131.57s (2C) +134.53d+134.57d+166.54s+168.55s (phthaloyl group). — EI-MS (200 °C), *m/z* (I%) 467.1154 (35), $C_{23}H_{21}N_3O_6S$, $M^{+\bullet}$; 408 (20); 382 (3); 353 (3); 322 (17); 320 (15), $[M-147]^+$; 266 (25); 263 (52); 261 (41); 207 (80); 166 (27); 164 (28); 147 (*100*), phthalimido; 104 (65), C_6H_4CO; 86 (70); 76 (55), C_6H_4; 43 (40), Ac^+.

Structure determination of compound **7a** - *Crystal Data.* Empirical formula: $C_{26}H_{28}N_4O_7S$ (one molecule of solvent DMF included), formula weight = 540.6. Colourless plate, approx size (mm) 0.08 x 0.20 x 0.35. Monoclinic space group $P2_1/n$ (No. 14). Unit cell dimensions a = 11.212(1), b = 9.328(1) c = 25.220(2) Å, β = 100.81(2)°, V = 72590.8(4) Å^3, Z = 4, D_X = 1.386 Mg/m^3, μ(Cu-$K\alpha$, λ=1.5418 Å) = 1.521 mm^{-1}, F(000) = 1136.

Data Collection. Enraf-Nonius CAD-4 diffractometer equipped with a graphite crystal monochromator, Cu-$K\alpha$ radiation, temperature: 296 K. θ range 3.0 to 77°. The ω-2θ scan technique was applied with variable scan speed 10.0 to 30.0°/min. in ω. The scan range (ω) was $\Delta\omega$ = 0.56 + 0.22 $tg\theta$°. The intensities of 3 standard reflections were monitored every 60 min. and these indicated an overall intensity decrease of 10.3%. An anisotropic decay correction was applied (min., max. and average correction factors were 0.99, 1.08 and 1.01). Index ranges: $-14 \le h \le 0$, $0 \le k \le 11$, $-31 \le l \le 31$. 4863 reflections were collected of which 4634 (R_{int} = 0.012) were independent. 3827 observed reflections ($F_o \ge 4.0\sigma(F)$) reflections were used in structure refinement.

Structure solution and refinement. The structure was solved by direct methods (SHELXS[11]), and was refined by full-matrix least-squares (SHELX-76[12]). The quantity minimized was $\Sigma w(F_o-F_c)^2$. Hydrogen atomic positions were generated from assumed geometries except H23 which was located in a difference map. Hydrogen atoms were included in the structure refinement as riding atoms. A common isotropic U was refined for the hydrogen atoms of the bulk molecule (0.084 Å^2) and another for those of the DMF solvent (0.252 Å^2). The weighting scheme applied was $w^{-1} = \sigma^2(F) + 0.0046F^2$. 345 parameters were refined. The final R indices were R = 0.048, wR = 0.082 for the observed, and R = 0.060, wR = 0.087 for all data. Goodness-of-fit = 1.04, largest and average Δ/σ are 0.533 and 0.112. Data-to-parameter ratio 11.1 : 1. The largest peak and deepest hole in the final difference map were 0.20 and -0.28 eÅ^{-3}.

Note. The solvent molecule is linked to the OH group *via* hydrogen bonding:

D - H ····· *A*

O23 - H23·····O1x

D-H: 1.02 Å; H···*A*: 1.67 Å; *D*···*A*: 2.653(4) Å; *D*-H···*A*: 160°.

(*d*) A methanolic (10 cm^3) solution of CAN (1.55 g, 2.8 mmol) was added within 20 min. to a solution of compound **5a** (452 mg, 1 mmol) in a mixture of acetonitrile (15 cm^3) and methanol (5 cm^3) as described

in (*a*). The mixture was stirred for 1 h at -5 °C and for 3 h at room temperature and evaporated to dryness at reduced pressure. The residue was taken up in ethyl acetate (40 cm^3), the solution washed successively with water (2x10 cm^3), saturated aqueous Na_2CO_3 (10 cm^3) and water (2x10 cm^3), dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The residue was purified by TLC (dichloromethane - acetone, 10:1) to furnish *(2*RS,*2a*RS,*3*RS*)-4-acetyl-3,9-dimethoxy-2-phthalimido-2,2a,3,4,5,6-hexahydro-1*H*-azeto[2,1-f][1,4,7]benzothiadiazonin-1-one* (**9a**) (260 mg, 53%; m.p. 266-268 °C) which proved identical (m.p., IR, ^1H NMR) with the product obtained by successive treatment of compound **7a** with thionyl chloride and methanol (see below). ν_{max} (KBr) 1770, 1710, 1650 cm^{-1}. — δ_H 1.75 (s, Ac), 2.82 (s, 3-OMe), 2.77m+3.49m (6-H_2), 3.43m+3.84m (5-H_2), 3.79 (s, 9-OMe), 5.27 (d, J=9.1, 3-H), 5.71 (d, J=5.3, 2-H), 5.84 (dd, J=5.3 and 9.1, 2a-H), 6.91 (dd, J_o=8.8, J_m=2.8, 10-H), 7.07 (d, J_m=2.8, 8-H), 7.86 (d, J_o=8.8, 11-H), 7.82+7.94 (m, 4xArH). — δ_C 21.78 ($NCOCH_3$), 33.73 (C-6), 42.49 (C-5), 54.26 (3-OMe), 55.53 (9-OMe), 55.80 (C-2), 60.58 (C-2a), 86.28 (C-3), 116.12 (C-10), 122.74 (C-8), 124.33 (C-11), 127.27 (C-7a), 131.51 (C-11a), 157.62 (C-9), 162.63 (C-1), 171.35 ($NCOCH_3$), 123.69d+124.09d+131.32s+131.46s+134.79d+134.82d+166.40s+168.97s (phthaloyl group).

(*e*) Compound **5c** (2.95 g, 7.3 mmol) was treated with CAN as described in (*a*) and (*c*). The mixture was stirred for 10 min. Ethyl acetate (120 cm^3) was added and the organic phase washed with saturated aqueous Na_2CO_3 (15 cm^3) and water (2x20 cm^3), dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The residue was purified by CC (dichloromethane - acetone, 3:1) to yield *(2*RS,*2a*RS,*3*RS*)-4-acetyl-2-allyloxycarbonylamino-3-hydroxy-9-methoxy-2,2a,3,4,5,6-hexahydro-1*H*-azeto[2,1-f][1,4,7]benzothiadiazonin-1-one* (**7c**) [1.43 g, 66%; m.p. 161 °C (ethyl acetate - acetonitrile - hexane)].

Found C, 52.95; H, 5.6; N, 9.6; S, 7.2. $C_{19}H_{23}N_3O_6S \cdot 1/2\ H_2O$ (430.5) requires C, 53.0; H, 5.6; N, 9.75; S, 7.45%. ν_{max} (KBr) 1750/1740 (d), 1695 cm^{-1}. — δ_H ($CDCl_3$+DMSO-d_6) 1.71 (s, Ac), 2.77+3.39 (J_{gem}=-14.6, J_{vic}=2.7, 2.5 and 12.4, 2.9, respectively, 6-H_2), 3.63+3.84 (J_{gem}=-14.4, J_{vic}=12.4, 2.7 and 2.9, 2.5, respectively, 5-H_2), 3.76 (s, OMe), 4.60+4.65 (*ABX*, J_{gem}=-13.0, J_{vic}=5.5 and 5.5, OCH_2), 5.19 (dd, J=9.0 and 5.2, 2-H), 5.22+5.34 (J_{gem}=-1.3, J_{cis}=10.5, J_{trans}=17.0, CH=CH_2), 5.49 (dd, J=9.4 and 4.8, 3-H), 5.60 (dd, J=9.4 and 5.2, 2a-H), 5.63 (br d, J=4.8, 3-OH), 5.94 (ddt, J=17.0, 10.5 and 5.5, C*H*=CH_2), 6.81 (dd, J_o=8.8, J_m=2.8, 10-H), 7.02 (d, J_m=2.8, 8-H), 7.42 (br d, J=9.0, 2-NH), 7.69 (d, J_o=8.8, 11-H). With the aid of ^1H-{^1H}NOE experiments the closeness of the 3-H proton to the acetyl-methyl and hydroxyl protons, of the 8-H proton to the methoxy and one of the 6-H_2 protons (at 3.39 ppm) as well as of the 2a-H proton to the 2-H and one of the 5-H_2 protons (at 3.63 ppm) was established. — δ_C ($CDCl_3$+DMSO-d_6) 21.87 ($NCOCH_3$), 34.43 (C-6), 43.21 (C-5), 55.39 (OMe), 59.21 (C-2), 61.99 (C-2a), 65.70 (OCH_2), 79.17 (C-3), 115.61 (C-10), 117.57 (CH=CH_2), 122.60 (C-8), 124.05 (C-11), 127.51 (C-7a), 131.95 (C-11a), 132.84 (*C*H=CH_2), 156.31 (O*C*ONH), 157.03 (C-9), 166.15 (C-1), 171.03 ($NCOCH_3$). — EI-MS (200 °C), *m/z* (I%) 421.1300 (38), $C_{19}H_{23}N_3O_6S$, $M^{+\bullet}$; 392 (3); 363 (2); 336 (5); 321 (4), [M-$C_3H_5O_2CNH$]$^+$; 281 (43), [M-$C_3H_5O_2CNH$-C=CO]$^+$; 208 (25); 207 (28); 192 (24); 166 (32); 86 (*100*); 44 (31); 43 (15); 41 (22), $C_3H_5^+$. — FAB-MS (NOBA matrix), *m/z* (I%) 422 (48), MH^+; 421 (60), $M^{+\bullet}$; 404 (*100*), [MH^+-18]; 281 (18). — FAB-MS/MIKE [MH^+], *m/z* (I%) 404 (*100*), [MH^+-18]; 281 (20), [MH^+-$C_3H_5O_2CNH$-C=CO].

Conversion of compound **7a** *into compound* **9a**

A solution of compound **7a** (470 mg, 1 mmol) in thionyl chloride (10 cm^3) was kept for 24 h in a refrigerator and evaporated to dryness at reduced pressure. The residue was taken up in anhydrous methanol (10 cm^3) and kept for 24 h at room temperature. The crystalline product [440 mg, 90%; m.p. 266-268 °C (from methanol - diethyl ether)] was filtered off and washed with methanol and diethyl ether. It proved identical (m.p., IR, ^1H NMR) with another sample of compound **9a**, obtained by treatment of compound **5a** in a mixture of acetonitrile and methanol with CAN (see above).

Found C, 59.8; H, 4.75; N, 8.55; S, 6.5. $C_{24}H_{23}N_3O_6S$ (481.5) requires C, 59.85; H, 4.8; N, 8.75; S, 6.65%. ν_{max} (KBr) 1775, 1720, 1660 cm^{-1}. — The ^1H and ^{13}C NMR spectra were identical with those of a sample of compound **9a** obtained starting with compound **5a** (see above). — EI-MS (170 °C), *m/z* (I%) 481 (52), $M^{+\bullet}$; 449 (7), $[M-32]^{+\bullet}$; 411 (6); 324 (8); 216 (30); 207 (16); 147 (25), $[C_6H_4(CO)_2NH]^{+\bullet}$; 58 (47); 43 (*100*), Ac^+. — FAB-MS (NOBA matrix), *m/z* (I%) 482 (31), $[MH^+]$; 481 (35, $[M^{+\bullet}]$; 450 (*100*), $[MH^+-32]$. — FAB-MS/MIKE $[MH^+]$, *m/z* (I%) 464 (45), $[MH^+-18]$; 450 (*100*), $[MH^+-32]$; 216 (20), $[MH^+-266]$.

Isomerization of compounds **7a** *and* **7c**

(*a*) A methanolic (100 cm^3) solution of compound **7a** (468 mg, 1 mmol) was refluxed for 3 h and evaporated to dryness at reduced pressure. The residue was purified by TLC (toluene - propan-2-ol, 2:1) to give *(2RS,3RS)-1-(2-acetylaminoethylthio-4-methoxyphenyl)-4-oxo-3-phthalimidoazetidine-2-carbaldehyde* (**8a**) (281 mg, 60%; m.p. 133 °C).

Found C, 58.8; H, 4.5; N, 8.85; S, 6.9. $C_{23}H_{21}N_3O_6S$ (467.5) requires C, 59.1; H, 4.55; N, 9.0; S, 6.85%. ν_{max} (KBr) 1760 sh, 1750 sh, 1725/1715 (d), 1690 cm^{-1}. — δ_H* 1.85 (s, Ac), 3.08+3.20 (J_{gem}=-13.8, J_{vic}=5.5, 6.2 and 5.5, 6.7, respectively, S-CH_2), 3.45 (m, CH_2NH), 3.86 (s, OMe), 4.92 (dd, J=6.2 and 2.2, 2-H), 5.88 (d, J=6.2, 3-H), 6.42 (br t, J=5.5, NH), 6.86 (dd, J_o=8.7, J_m=2.7, 5'-H), 7.05 (d, J_m=2.7, 3'-H), 7.61 (d, J_o=8.7, 6'-H), 7.75-7.95 (m, 4xArH, phthaloyl group), 9.92 (d, J=2.2, 2-CHO). — δ_C* 22.89 ($NHCOCH_3$), 33.81 (S-CH_2), 38.82 (CH_2NH), 55.80 (OMe), 56.28 (C-3), 65.56 (C-2), 113.32 (C-5'), 116.13 (C-3'), 127.7 (C-2'), 128.59 (C-6'), 133.7 (C-1'), 159.87 (C-4'), 164.14 (C-4), 170.73 ($NHCOCH_3$), 196.67 (CHO), 124.06d+131.42s+134.89d+ 166.88s (phthaloyl group). — EI-MS (190 °C), *m/z* (I%) 467 (32) $M^{+\bullet}$; 408 (24); 382 (4); 351 (3); 337 (3); 320 (12), $(M-147)^+$; 292 (3); 266 (21); 261 (30); 221 (11); 207 (*100*); 192 (18); 178 (15); 147 (55); 132 (4); 104 (52); 86 (90); 76 (38); 43 (30), Ac^+.

(*b*) 2,4-Dinitrophenylhydrazine (20 mg, 0.1 mmol) and concd H_2SO_4 (5 mm^3) were successively added to a methanolic (10 cm^3) solution of compound **8a** (47 mg, 0.1 mmol). The mixture was allowed to stand for 1 h and evaporated to dryness at reduced pressure. The residue was worked up by TLC (toluene - propan-2-ol, 9:2) to give the 2,4-dinitrophenylhydrazone (50 mg, 77%; yellow crystals, m.p. 125 °C) of compound **8a**.

Found C, 53.8; H, 3.9; N, 15.1; S, 4.85. $C_{29}H_{25}N_7O_9S$ (647.6) requires C, 53.8; H, 3.9; N, 15.15; S, 4.95%.

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* Primed locants refer to the *N*-aryl subtituent

ν_{max} (KBr) 1800, 1750, 1695 cm^{-1}. — δ_H* 1.86 (s, Ac), 3.10+3.24 (J_{gem}=-13.8, J_{vic}=5.5, 6.2 and 5.5, 6.7, respectively, S-CH_2), 3.38-3.55 (m, CH_2NH), 3.83 (s, OMe), 5.28 (dd, J=7.0 and 5.5, 2-H), 5.94 (d, J-5.5, 3-H), 6.53 (br t, J=5.9, CH_2NH), 6.82 (dd, J_o=8.7, J_m=2.6, 5'-H), 7.04 (d, J_m=2.6, 3'-H), 7.42 (d, J_o=8.7, 6'-H), 7.70 (d, J=7.0, 2-CH=N), 7.77 (d, J_o=9.4, 6''-H), 7.77-7.94 (m, 4xArH, phthaloyl group), 8.23 (dd, J_o=9.4, J_m=2.5, 5''-H), 9.01 (d, J_m=2.5, 3''-H), 11.10 (br s, Ar-NH).

(*c*) A methanolic (40 cm^3) solution of compound **7c** (430 mg, 1 mmol) was kept for 1 week at room temperature and worked up by CC (EtOAc) to give *(2*RS,*3*RS*)-2-acetylaminoethylthio-4-methoxyphenyl)-3-allyloxycarbonylamino-4-oxoazetidine-2-carbaldehyde* **8c** (295 mg, 70%; m.p. 145-148 °C).

Found C, 54.2; H, 5.55; N, 9.85, S, 7.5. $C_{19}H_{23}N_3O_6S$ (421.5) requires C, 54.15; H, 5.5; N, 9.95; S, 7.6%. ν_{max} (KBr) 1790, 1750 sh, 1720, 1660 cm^{-1}. — δ_H† 1.83 (s, Ac), 3.02+3.16 (J_{gem}=-13.8, J_{vic}=6.1, 5.5 and 6.5, 5.5, respectively, S-CH_2), 3.41 (m, CH_2NH), 3.82 (s, OMe), 4.58-4.64 (m, OCH_2), 4.94 (dd, J=5.6 and 1.4, 2-H), 5.24 (dd, J=5.6 and 7.5, 3-H) 5.25+5.31 (J_{gem}=-1.3, J_{cis}=10.5, J_{trans}=17.0, CH=CH_2), 5.68 (br d, J=7.5, 3-NH), 5.89 (m, CH=CH_2), 6.45 (br t, J=5.8, CH_2NH_2), 6.79 (dd, J_o=8.7, J_m=2.7, 5'-H), 6.98 (d, J_m=2.7, 3'-H), 7.52 (d, J_o=8.7, 6'-H), 9.82 (d, J=1.4, 2-CHO). — δ_C† 22.86 (NHCOCH_3), 33.84 (S-CH_2), 38.82 (CH_2NH), 55.74 (OMe), 61.25 (C-3), 66.58 (OCH_2), 66.70 (C-2), 113.21 (C-5'), 116.14 (C-3'), 118.44 (CH=CH_2), 127.91 (C-2'), 128.52 (C-6'), 131.87 (CH=CH_2), 133.20 (C-1'), 155.65 (OCONH), 159.58 (C-4'), 165.51 (C-4), 170.87 (NH$COCH_3$), 197.09 (CHO). — EI-MS (170 °C), *m/z* (I%) 421 (67), $M^{+\bullet}$; 363 (3); 336 (4), $[M-85]^+$; 281 (52), $[M-C_3H_5O_2CNH-C=CO]^+$; 222 (9); 208 (29); 207 (25); 192 (31); 166 (39); 123 (3); 86 (*100*); 44 (31); 43 (18), Ac^+; 41 (26), $C_3H_5^+$. — FAB-MS (NOBA matrix), *m/z* (I%) 422 (*100*), MH^+; 421 (17), $M^{+\bullet}$; 321 (9), $[MH^+-C_3H_5O_2CNH_2]$; 281 (17), $[MH^+-C_3H_5O_2CNH-CH=CO]$. — FAB-MS/MIKE ($MH^+$), *m/z* 363 (30), 321 (*100*), 281 (25), $[MH^+-141]$, 86 (18).

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* Primed and doubly primed locants refer to the lactam *N*-substituent and the dinitrophenyl group, respectively

† Primed locants refer to the *N*-aryl substituent

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