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Simple and Condensed β-Lactams. Part 27.[1] Reaction of 1-(4-Methoxyphenyl)-4-(tetrazol-5-yl)azetidin-2-one and 1-(4-Methoxyphenyl)-5-(tetrazol-5-yl-methyl)pyrrolidin-2-one with Cerium(IV) Ammonium Nitrate (CAN)

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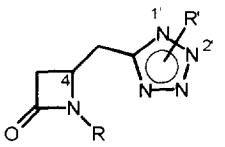
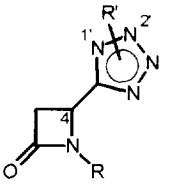
Abstract: Treatment of pyrrolidinone **3a** with CAN under the usual conditions leads to formation of spiro compound **12**, rather than to *N*-demethoxyphenylation. A study of the reactions of compound **12** with sodium chloride and sodium iodide furnished the proof for our assumption that the related non-isolable compounds **6** and **11** are the intermediates of the anomalous reactions of compounds **1a** and **2a**, respectively, with CAN.

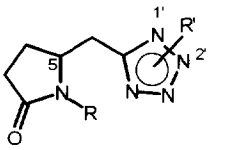
In Part 14[2] of the present series 1-(4-methoxyphenyl)-4-(tetrazol-5-ylmethyl)azetidin-2-one (**1a**) has been reported to react anomalously with cerium(IV) ammonium nitrate (CAN); *viz.* compound **1a** failed to yield, under the usual reaction conditions, the *N*-deprotected derivative **1b**. Instead, when the reaction mixture was treated, prior to work-up, with sodium chloride or iodide, 1-(3-chloro-4-hydroxyphenyl) (**1g**) and 1-(4-hydroxyphenyl) derivatives (**1h**), respectively, were formed as the main products. In contrast, compound **1e**[2] (as well as its 1'-[3] and 2'-diphenylmethyl, 1'- and 2'-benzyl analogues[2]) reacted normally with CAN to afford compound **1f** and its analogues, respectively.The contrasting behaviour of compounds **1a** and **1e** was rationalized in the following way.[2] (Our original reasoning is reproduced here in slightly modified and extended form.) In agreement with the currently accepted mechanism of *N*-de(4-methoxyphenylation)[4] compounds **1a** and **1e** were assumed to undergo successive oxidation, hydroxy-demethoxylation and deprotonation to afford compounds **4a** and **4e**, respectively, as the first intermediates (Scheme). Quinone-iminium intermediates **4** are normally attacked by water molecules at C-1 of the quinone-iminium moiety which ultimately leads to the formation of *N*-demethoxyphenylated products and *p*-benzoquinone[4] as *e.g.* in the case of intermediate **4e** affording compound **1f** as a result. Intermolecular nucleophilic attack by a water molecule in the case of intermediate **4a** is, however, thought to be suppressed because of the much faster intramolecular nucleophilic attack at the same site, led by one of the tetrazole nitrogen atoms in sterically favourable position.[5] This should lead to the formation of spiro compound **5a** and thence, by proton loss from the highly acidic tetrazolium N^+H group, to **6** which is thought to be the main component of the triple equilibrium **4a** ⇌ **5a** ⇌ **6**. Since the *N*-substituted compounds **5e** do not contain acidic protons, formation of stable neutral compounds related to **6** is impossible in these cases. As a result, intermediates **4e** (which are thought to be in equilibrium with their cyclic isomers **5e**) readily react with water to afford the *N*-deprotected derivatives **1f**.



1
(a, f, g)*



2
(a, d, f, g, k, l)*



3
(a, c, e-h, k-n)*

1-3

	R	R'		R	R'
a	4-$MeOC_6H_4$	H	**i**	3-Cl-4-HOC_6H_3	2'-Me
b	H	H	**j**	4-HOC_6H_4	2'-Me
c	4-$MeOC_6H_4$	1'-Me	**k**	3-Cl-4-$MeOC_6H_3$	1'-Me
d	H	1'-Me	**l**	3-Cl-4-$MeOC_6H_3$	2'-Me
e	4-$MeOC_6H_4$	2'-Me	**m**	3-Cl-4-MeO-5-$O_2NC_6H_2$	1'-Me
f	H	2'-Me	**n**	3-Cl-4-MeO-5-$O_2NC_6H_2$	2'-Me
g	3-Cl-4-HOC_6H_3	H	**o**	3-Cl-4-HO-5-$O_2NC_6H_2$	H
h	4-HOC_6H_4	H			

On the other hand, treatment of oxidation mixtures of compound **1a** with sodium chloride should lead, as a consequence of nuclophilic attack by a chloride anion at C-3 of the quinone-iminium moiety of intermediate **4a** or of C-3' of intermediate **5a** or even of **6** (in the last case with concomitant protonation),† to intermediate **7a** and thence by prototropy to product **1g**.[2] ‡ Similarly, treatment of oxidation mixtures of compound **1a** with sodium iodide should lead, as a result of transfer of two electrons ($2I^- \rightarrow 2e + I_2$) to intermediates **4a**, **5a** and/or **6** (in the last case followed by protonation) to the formation of phenolate anion **8a** and thence, by protonation, to hydroxyphenyl derivative **1h**.

In order to gain support for the mechanism suggested for the anomalous reaction of compound **1a** with CAN, various attempts at isolation or, at least, spectroscopical detection of key-intermediate **6** were carried out but all our attempts failed.

Now we report our studies aiming to extend the scope of the anomalous reaction of compound **1a** with CAN to some related compounds, on the effect of structural variations on the reactivity, on the isolation in one case of an analogue of compound **6** and on some observations concerning the reactivity of this analogue.

Successive treatment of compound **2a** (see below for its preparation) with CAN and, prior to work-up, with sodium chloride afforded compound **2g** in 52% -optimized yield (which may be compared with the 37% yield of compound **1g** isolated on similar treatment of compound **1a**) while, when sodium chloride treatment

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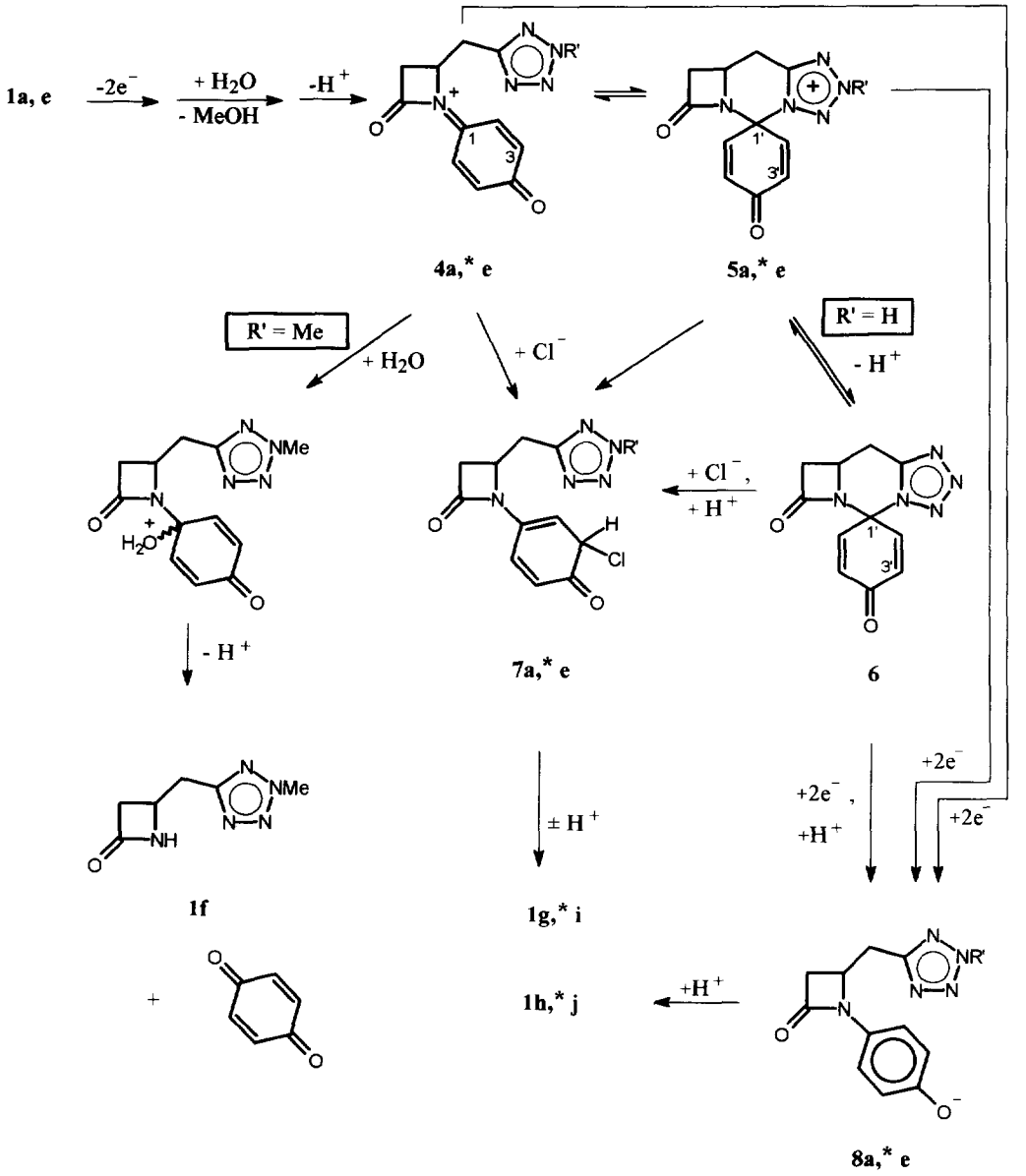
* Compounds described in this paper

† The isolated stable ring homologue **12** (see below) of compound **6** has been found to react with chloride anions, although slowly, even in the absence of added acid.

‡ Reaction of quinone-iminium intermediates **4** with water has been found not to be instantaneous.[6] Therefore we believe that, had the reaction mixtures containing intermediates **4e** been treated with sodium chloride, mixtures of compounds **1f** and **1i** would have been obtained. Analogusly, had these reaction mixtures been treated with sodium iodide, mixtures of compounds **1f** and **1j** would have been obtained.



Scheme. Mechanism of the reaction of β-lactams **1a** and **1e** with CAN and with CAN followed by sodium chloride and iodide, respectively. **a**, **g**, **h** : R' = H, **e**, **i**, **j** : R' = Me

* The 1'-*H* tautomeric structure seems equally well possible for these compounds

was omitted, only tars were isolated rather than the demethoxyphenylation product **2b**. Because of the free phenolic OH and the tetrazole NH groups we did not succeed in obtaining a completely pure sample of compound **2g** by chromatography. In another experiment the reaction mixture obtained by successive treatment of compound **2a** with CAN and sodium chloride was therefore treated, prior to work-up, with excess ethereal diazomethane. The resulting two isomeric *N,O*-dimethyl derivatives **2k** and **2l** were then isolated by chromatography in pure form. The positions of the *N*-methyl groups of compounds **2k** and **2l** were deduced from a comparison of the chemical shifts of the *N*-methyl signals of the more (m.p. 170°C; δ 4.14) and less polar isomers (m.p. 101°C; δ 4.36) with those of the related isomers **2d** (more polar 1'-Me derivative, δ 4.13) and **2f** (less polar 2'-Me derivative, δ 4.37 ppm) whose structures have been unequivocally assigned (see below). Therefore of isomers **2k** and **2l** the more polar isomer has to be the 1'-methyl (**2k**) and the less polar the 2'-methyl derivative (**2l**).

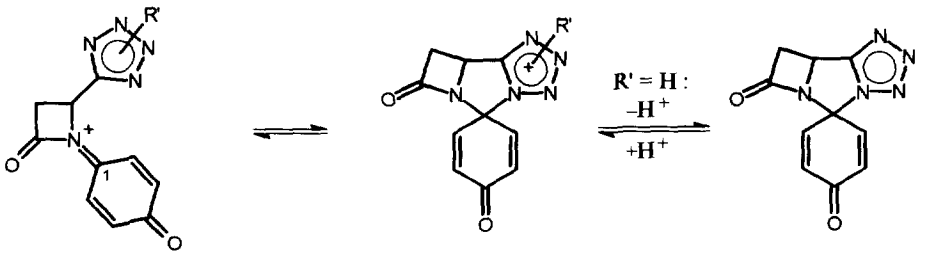
When the reaction mixture obtained from compound **2a** with CAN was treated, prior to work-up, with ethereal diazomethane, the *N*-demethoxyphenylated *N'*-methyl isomers **2d** and **2f** were obtained to our surprize; the total yield was 58% after chromatographic work-up. The less (m.p. 101-102°C) and the non-crystalline more polar isomers were assigned the 2'- (**2f**) and 1'-methyl structures (**2d**) on the basis of a NOE, observed on the 4-H signal on irradiation of the *N*-methyl signal of the more polar isomer. Successive treatment with CAN and diazomethane of compound **1a** similarly afforded compound **1f**[2] in 22% yield. [Again, the yield in the tetrazolylazetidinone series (58% **2d**+**2f**) was found to be higher than in the (tetrazolylmethyl)-azetidinone series (22% **1f**).] The chemical shift of the *N*-methyl signal of compound **1f** (4.31 ppm[2]) compares well with those of the less polar isomers (4.37 and 4.36 ppm) assigned the 2'-methyl structures **2f** and **2l**, respectively, which supports these structure assignments.

Formation of compound **2g** on successive treatment of compound **2a** with CAN and sodium chloride is analogous to transformation **1a** → **1g**[2] brought about by similar treatment, and is thought to involve the intermediacy of triple equilibrium **9a** ⇌ **10a** ⇌ **11** (which is analogous to triple equilibrium **4a** ⇌ **5a** ⇌ **6**) Unfortunately, all attempts to isolate compound **11** from, or at least to detect it in the reaction mixture again failed, similarly as in the case of assumed intermediate **6**.[2] When the oxidation mixture containing compound **2g** is treated with diazomethane, *N*-methyl derivatives **2k** and **2l** are formed in agreement with expectation.

On the other hand, formation of *N*-deprotected *N'*-methyl isomers **2d** and **2f** on successive treatment of compound **2a** with CAN and diazomethane, as well as of compound **1f** on similar treatment of compound **1a** was unexpected. Conversion of cations **9a** (the initial product of the reaction of compound **2a** with CAN) and **10a** or of the neutral form **11** into compounds **2d** and **2f** comprises three changes, *viz.* (*i*) *N*-methylation, (*ii*) adduct formation with water, followed by (*iii*) elimination of the lactam nitrogen substituent. These three changes are thought to take place in the order given since, if methylation were preceded by adduct formation, formation of compound **2b** would have to take place on CAN treatment of compound **2a** omitting subsequent treatment with diazomethane; all our attempts to isolate compound **2b** under these conditions, however, failed. Reaction of cations **9a** and **10a** with diazomethane or, possibly, of the neutral form **11** with protonated diazomethane*† should lead to the formation of mixtures of the isomeric *N*-methyl derivatives **9b** and their ring tautomers **10b**, respectively. Subsequent attack of water molecules at C-1 of the *N*-substituents of isomers

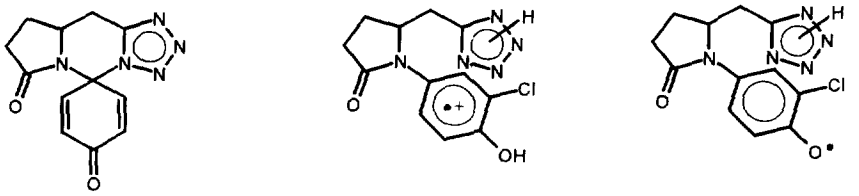
* The reaction mixtures obtained by treatment of compounds **1a-3a** are strongly acidic.

† The isolated stable analogue **12** of compound **11** was found not to furnish *N*-methyl derivatives on treatment with diazomethane in dichloromethane in the absence of added acid.



9 **a** : R' = H ; **b** : R' = Me **10** **11**

9b, or at the spiro carbon atoms of isomers **10b** should then lead, with loss of a proton and benzoquinone, to isomers **2d** and **2f**, similarly as shown for transformation **4e** → **1f** in the Scheme. Formation of compound **1f** from compound **1a** on successive treatment with CAN and diazomethane may be rationalized similarly.



12 **13** **14**

As expected and in contrast to its 2'-methyl analogue **3e** which was normally *N*-demethoxyphenylated by CAN, *N'*-unsubstituted compound **3a**, a ring homologue of compound **1a** (for the preparation of these compounds, see below) reacted anomalously with CAN and furnished, under the usual conditions, spirocyclic compound **12** in crystalline form. Compound **12** is an analogue of postulated intermediates **6** and **11** and proved comparatively stable. Moreover, it reacted with sodium chloride and iodide in exactly analogous manner as postulated for the corresponding reactions of intermediate **6** (see Scheme). The reactivity of compound **12** towards these reagents was studied both by treating isolated compound **12** with sodium chloride and sodium iodide in the presence of added acid* or by subjecting reaction mixtures resulting by CAN treatment of compound **3a** directly, *i.e.* without isolation of product **12**, to the same treatment.† In the course of these studies it was noted that work-up of some reaction mixtures resulting from such treatments, notably the separation and purification by chromatographic methods of their components containing free phenolic hydroxyl groups presented difficulties. Therefore these product mixtures were treated in several cases, prior to work-up, with diazomethane. This brought about methylation both of phenolic hydroxyl and tetrazole NH groups, allowing the resulting methyl derivatives to be separated and purified much easier than their non-methylated precursors.

Thus, successive treatment of compound **12** with sodium chloride in the presence of hydrochloric acid and with diazomethane afforded the two isomeric 1-(3-chloro-4-methoxyphenyl)-5-(*N*-methyltetrazol-5--ylmethyl)pyrrolidin-2-ones **3k** and **3l**, the dimethylation products of intermediate **3g**, in 66% total yield. When diazomethane treatment of the oxidation mixture was omitted, compound **3g** itself was obtained but, owing to

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* In the absence of added acid compound **12** reacts very slowly with chloride anions.

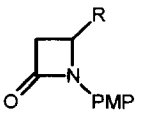
† Since the oxidation mixtures in question were strongly acidic, addition of acid proved unnecessary in the latter case.

its free OH and NH groups, it could not be purified completely. Treatment of compound **12** with sodium iodide in the presence of dilute sulfuric acid, on the other hand, afforded a somewhat impure sample of *N*-(4-hydroxyphenyl) derivative **3h** whose main component proved identical with a pure sample of compound **3h** obtained *via* non-isolated compound **12** (see below).

Successive treatment of compound **3a** with CAN, sodium chloride and diazomethane afforded the two isomeric 1-(3-chloro-4-methoxy-5-nitrophenyl)-5-(*N*-methyltetrazol-5-ylmethyl)pyrrolidinones **3m** and **3n** (in 60% total yield), formed by methylation of hydroxy derivative **3o**, while successive treatment of compound **3a** with CAN and sodium iodide afforded compound **3h**. Nitro derivatives related to compound **3o** have been obtained by CAN treatment of 1-(4-methoxyphenyl)azetidin-2-ones before.[6] Similarly as in the previous cases, formation of compound **3o** is thought to take place by classical (*i.e.* S_E-Ar type*) or non-classical nitration of initially formed 1-(3-chloro-4-hydroxyphenyl) derivative **3g**. The non-classical reaction would involve radical cations **13**, the one-electron oxidation products of compound **3g**, and/or radicals **14**, formed by deprotonation of the radical cations, as the intermediates.

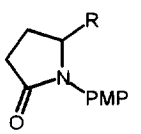
Preparation of compounds **2a**, **3a** *and* **3e**

Compound **2a** was synthesised starting with compound **15a**.[7] Swern oxidation of the latter afforded carbaldehyde **15b** which was converted *via* a mixture of its *Z*- and *E*-oximes (**15c**) into nitrile **15d**. Reaction of the nitrile with aluminium triazide (prepared *in situ* from aluminium trichloride and sodium azide[8]) finally compound **2a** in excellent yield.



15†

a	R = CH_2OH
b	R = CHO
c	R = CH=N〰OH
d	R = CN



16†

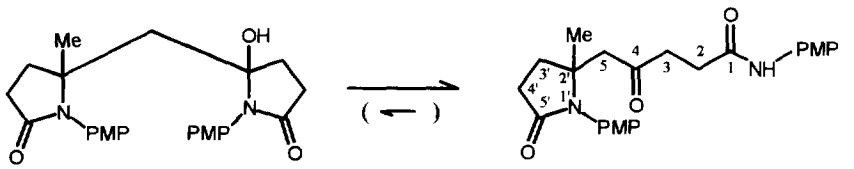
a	R = CO_2Me
b	R = CH_2OH
c	R = CH_2O_3SMe
d	R = CH_2I
e	R = CH_2N

The starting compound used for the preparation of compound **3a** was dimethyl 2-bromopentanedioate.[9] Condensation of the latter with *p*-anisidine afforded methyl 5-oxopyrrolidine-2-carboxylate **16a** in moderate yield. Ester **16a** was reduced with $NaBH_4$ to hydroxymethyl derivative **16b** in excellent yield. O-Methylsulfonylation, followed by reaction with sodium iodide afforded iodomethyl derivative **16d** *via* methanesulfonate **16c**. Reaction of compound **16d** with sodium cyanide afforded, in addition to the desired nitrile **16e** (41%), dimeric compound **17b** (20%). Compound **17b** may formally be derived by assuming elimination of hydrogen iodide from iodomethyl derivative **16d**, followed by (probably hydroxide ion catalyzed) head-to-tail coupling of two molecules of the resulting methylene pyrrolidinone with concomitant addition of water and, finally opening of the hydroxypyrrolidinone ring of compound **17a**. Nitrile **16e** was converted into compound **3a** by the Arnold - Thatcher method.[8] Treatment of compound **3a** with diazomethane afforded

* The oxidation mixtures are strongly acidic and contain nitrate ions, *i.e.* nitric acid.

† Racemic compounds, PMP= 4-methoxyphenyl

isomeric *N'*-methyl derivatives **3c** and **3e** in 30 and 68% yields, respectively. (The isomeric N'-methyl derivatives were indentified on the basis of a NOE study.)



17a **17b**

In conclusion, we succeeded in isolating spiro compound **12** from reaction mixtures obtained by treatment of (tetrazolylmethyl)pyrrolidinone **3a** with CAN, studied the reactions of compound **12** with sodium chloride and iodide, and thereby proved that compound **12** and its ring homologues **6** and **11**, respectively, are intermediates of the anomalous reactions of compounds **1a**, **2a** and **3a** with CAN.

EXPERIMENTAL

The reactions were, in general, monitored by t.l.c. (Kieselgel $PF_{254+366}$; solvents are given in parentheses; detection: UV light or I_2, tungsto- or molybdophosphoric acid as developing agents) and were allowed to go at least very nearly to completion. Unless otherwise stated, $MgSO_4$ was used as the drying agent. Evaporations to dryness were carried at reduced pressures (2.6-3.3 kPa) unless otherwise stated. For column chromatographic (c.c.) separations Kieselgel G or H, Merck, were used as the adsorbents; solvents are given in parentheses; solvent dichloromethane will be abbreviated as DCM.

Melting points were determined on a Kofler hot-stage melting point apparatus. IR spectra were recorded on a Specord-75 (Zeiss, Jena) spectrometer. NMR spectra were obtained with a Varian XL-400 spectrometer in DMSO-d_6 – $CDCl_3$ solutions, unless otherwise stated, and with TMS as the internal reference. Selected δ values are given in ppm, coupling constants in Hz. EI and + FAB mass spectra (selected *m/z* values are given) were obtained with an MS-902 instrument equipped with a direct inlet system at 70 C and with a VG ZAB-2 SEQ spectrometer using glycerol as the matrix, respectively.

Reactions of compound **1a** *with CAN followed by treatment with sodium chloride and diazomethane, respectively.*

(*a*)* An aqueous (49 cm^3) solution of CAN (5.8 g, 10.5 mmol) was added dropwise to compound **1a**[2] (0.91 g, 3.5 mmol) in acetonitrile (42 cm^3) with continuous stirring at -5°C. Stirring was continued for 1 1/4 h at this temperature (t.l.c.: dichloromethane – methanol, 7:2). NaCl (*ca* 18 g) was then added until the mixture was saturated, and stirring was continued for 45 min. The two phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed successively with saturated aqueous Na_2CO_3, 10% aqueous $NaHSO_3$, saturated aqueous Na_2CO_3 solutions and water, dried and evaporated to dryness to afford a crude product (0.36 g, 36.7%). The latter was purified by trituration with acetone to afford (RS)-*1-(3-chloro-4-hydroxyphenyl)-4-(tetrazol-5-ylmethyl)azetidin-2-one* (**1g**) in almost pure form [0.2 g, 20.4%; m.p.; ν_{max} (KBr), δ_H as described in ref. 2].

* This is a correction of the earlier description[2] of the method for the preparation of compound **1g**

(*b*) CAN (2.63 g, 4.82 mmol) in water (30 cm^3) was added dropwise to compound **1a**[2] (0.50 g, 1.9 mmol) in acetonitrile (30 cm^3) with continuous stirring at -5°C. The mixture was stirred for 5 h at -5°C. Since considerable amounts of unchanged compound **1a** were present at this point (t.l.c.), another portion of CAN (1.0 g, 1.9 mmol) in water (10 cm^3) was added. Stirring was continued for 30 min at -5°C, during which period most of compound **1a** was consumed. Freshly prepared excess ethereal diazomethane solution was added, the two phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried and evaporated to dryness. The residue was worked up by t.l.c. (DCM – acetone, 7:3) to afford (methyltetrazolylmethyl) azetidinone **1f** [0.07 g, 22%; ν_{max} (film) 3250 br, 1760/1730 cm^{-1}] as an oil which proved identical with an authentic sample.[2]

Reactions of tetrazolylazetidin-2-one **2a** *with CAN*

(*a*) An aqueous solution (50 cm^3) of CAN (5.8 g, 10.5 mmol) was added dropwise to a solution of compound **2a** (0.86 g, 3.5 mmol) in acetonitrile (42 cm^3) with continuous stirring at -10 – -5°C. Stirring was continued at this temperature for 1.5 h (t.l.c.: DCM – methanol, 7:3) and the reaction mixture was divided into two equal parts.

Ethyl acetate (20 cm^3) and NaCl (9.0 g) were added to the first half and the mixture was stirred for 3/4 h at room temperature. The two phases were separated and the aqueous phase was extracted with a 1:1 (v/v) mixture of ethyl acetate and acetonitrile. The combined organic phases were successively washed with 10% aqueous $NaHSO_3$ solution and water, dried and evaporated to dryness. The dry residue (0.42 g) was purified by t.l.c. (DCM – methanol, 7:3) to afford *1-(3-chloro-4-hydroxyphenyl)-4-tetrazol-5-yl)azetidin-2-one* **2g** [0.24 g, 51.7%; m.p. 203°C (from methanol); found: $M^{+\cdot}$, 265.0359; $C_{10}H_8ClN_5O_2$ requires: 265.0366; ν_{max} (KBr) 3500-3000br (with several local maxima), 1745 cm^{-1}; δ_H* (60°C) 3.44+3.47 *AB*X (14.5, 5.0, 3.2; 3-H_2), 5.36dd (5.0, 3.2; 4-H), 6.8d (8.6; 5'-H), 7.08dd (8.6, 2.5; 6'-H), 7.47d (2.5; 2'-H); *m/z* (rel. intensity, %; 190°C) 265 (100; $M^{+\cdot}$), 223 (2.1; M - CH_2CO), 169 (3.3; OCN-C_6H_3ClOH)] slightly contaminated, among others, with unchanged starting **2a**.

(*b*) Ethyl acetate (20 cm^3) was added to the second half of the original reaction mixture and the two phases were separated. The aqueous phase was extracted with a 1:1 (v/v) mixture of acetonitrile and ethyl acetate. The combined organic phases were washed successively with saturated aqueous Na_2CO_3, 10% aqueous $NaHSO_3$ and water, dried and evaporated to dryness to afford a tarry product (0.13 g).

(*c*) The organic phase, obtained by successive treatment of compound **1a** with CAN and NaCl, followed by extraction as described in (*a*) was dried, treated with excess freshly prepared ethereal diazomethane solution and evaporated to dryness. The residue was worked up by c.c. (DCM – acetone, 7:1) to afford *1-(3-chloro-4--methoxyphenyl)-4-(2-methyltetrazol-5-yl)azetidin-2-one* (**2l**) [45%; m.p. 101°C; found: $M^{+\cdot}$ 293.0671; $C_{12}H_{12}ClN_5O_2$ requires: 293.0680; ν_{max} (KBr) 1780 cm^{-1}; δ_H ($CDCl_3$)* 3.52+3.61 (2xdd; 14.8, 2.7 and 14.8, 5.5, respectively; 3-H_2), 3.84s (OMe), 4.36s (*N*-Me), 5.33dd (5.5, 2.7, 4-H), 6.83d (8.8; 5'-H), 7.23dd (8.8, 2.6; 6'-H), 7.49d (2.6; 2'-H)] and *1-(3-chloro-4-methoxyphenyl)-4-(1-methyltetrazol-5-yl)azetidin-2-one* (**2k**) [11.7%; m.p. 170°C; found: $M^{+\cdot}$ 293.0671; $C_{12}H_{12}ClN_5O_2$ requires: 293.0680; ν_{max} (KBr) 1780 cm^{-1}; δ_H* 3.34+3.75 (2xdd, 15.1, 2.6 and 15.1, 5.8, respectively; 3-H_2), 3.86s (OMe), 4.14s (*N*-Me), 5.62dd (5.8, 2.6; 4-H), 6.88d (8.8; 5'-H), 7.05dd (8.8, 2.5; 6'-H), 7.43d (2.5; 2'-H)] in the order of decreasing R_f values.

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

(*d*) An aqueous solution (30 cm^3) of CAN (2.8 g, 5.2 mmol) was added to a solution of compound **2a** (0.5 g, 2.0 mmol) in acetonitrile (30 cm^3) as described in (*a*). The mixture was then stirred at -5°C until, according to t.l.c. (DCM – methanol, 7:3), compound **2a** was consumed (2 h). Excess freshly prepared ethereal diazomethane solution (60 cm^3, 70 mmol) was slowly added. The two phases were separated and the aqueous phase was extracted with a 1:1 (v/v) mixture of ethyl acetate and acetonitrile. The combined organic phases were dried and evaporated to dryness. Work-up of the reaction mixture by t.l.c. (DCM – acetone, 7:2) afforded two non-identified non-β-lactamic products (both less than 0.05 g), *4-(2-methyltetrazol-5-yl)azetidin--2-one* (**2f**) {0.12 g, 38.5%; m.p. 101-102°C; found: $M^{+\cdot}$ 153.0654 [calculated from the $(M+H)^+$ ion of the FAB spectrum]; $C_5H_7N_5O$ requires: $M^{+\cdot}$ 153.0651; ν_{max} (KBr) 3200 br, 1760 cm^{-1}; δ_H ($CDCl_3$) 3.37+3.52 (*ABX*; 14.8, 2.7, 5.4; long range coupling with the NH group, 1.4 and 2.1, respectively; 3-H_2), 4.37s (*N*-Me), 5.00dd (2.7, 5.4; 4-H), 6.72 br (NH)} and *4-(1-methyltetrazol-5-yl)azetidin-2-one* (**2d**) {0.06 g, 19%; gummy product, slightly contaminated with an unidentified impurity; found: $M^{+\cdot}$ 153.0650 [calculated from the $(M+H)^+$ ion of the + FAB spectrum]; $C_5H_7N_5O$ requires: $M^{+\cdot}$, 153.0651; ν_{max} 3250 br, 1760 cm^{-1}; δ_H ($CDCl_3$) 3.36+3.62 (2xddd; 15.2, 2.8, 1.2 and 15.2, 5.5, 2.4, respectively; 3-H_2), 4.13 (*N*-Me), 5.05dd (5.5, 2.8; 4-H), 7.14 br (NH); NOE: 4.13 (*N*-Me) → 5.05 (4-H)} in the order of decreasing R_f values.

Reactions of pyrrolidin-2-one **3a** *with CAN*

(*a*) Cerium(IV) ammonium nitrate (3.3 g, 6 mmol) in water (28 cm^3) was added dropwise to compound **3a** (0.46 g, 1.68 mmol) in acetonitrile (28 cm^3) with continuous stirring and cooling at such a rate that the temperature did not exceed -5°C (*ca* 10 min). Stirring was continued for 45 min at this temperature. Ethyl acetate (30 cm^3) was added and the two phases were separated. The aqueous phase was extracted with ethyl acetate. The combined organic phases were dried and evaporated to dryness. The residue was worked up by c.c. (Kieselgel 60 H, Merck; DCM – acetone, 7:0.5). The combined fractions containing the desired product were evaporated to dryness. The residue was triturated with diethyl ether to afford *(RS)-Spiro{8,9,9a,10--tetrahydro-5H,7H-pyrrolo[1,2-c]tetrazolo[5,1-f]pyrimidine-5,1'-cyclohexa-2',5'-diene-7,4'-dione}* (**12**) {0.26 g, 60%; m.p. 195°C (dec.); found: $M^{+\cdot}$, 257.0904 [calculated from the mass of the $(M+H)^+$ ion of the +FAB spectrum]; $C_{12}H_{11}N_5O_2$, requires: 257.0912; ν_{max} (KBr) 1720, 1690, 1650 cm^{-1}; δ_H (60°C) 1.99m (9-H_A), 2.4-2.6m (9-H_B + 8-H_2), 3.11+3.54, *ABX* (16.2, 11.0, 3.7; 10-H_2), 4.41m (9a-H), 6.4d (~ 9.5; 3'-H + 5'-H), 6.89m + 7.00m (2'-H + 6'-H); δ_C 24.62 (C-9), 27.67 (C-10), 30.86 (C-8), 52.09 (C-9a), 69.75 (C-5), 129.17 + 129.82 (C-3' + C-5'), 139.58 + 143.84 (C-2' + C-6'), 150.76 (C-10a), 173.24 (C-7), 184.07 (C-4')}.

(*b*) Cerium(IV) ammonium nitrate (12.3 g, 22.5 mmol) in water (140 cm^3) was dropwise added to compound **3a** (2.05 g, 7.5 mmol) in acetonitrile (140 cm^3) at -5°C. The mixture was stirred at this temperature until, according to t.l.c. (DCM – methanol, 7:2), compound **3a** was consumed, and divided into three equal parts.

The *first part* of the reaction mixture was extracted with ethyl acetate, the combined organic phases were dried (Na_2CO_3) and worked up by t.l.c. (DCM – acetone, 7:3) to afford compound **12** (0.53 g, 83%) which proved identical (m.p., IR) with the sample obtained as described in (*a*).

The *second part* of the reaction mixture was saturated with NaCl, and stirred at room temperature until compound **12** was consumed (*ca* 48 h). The mixture was extracted with ethyl acetate. The combined organic

phases were dried, treated with freshly prepared ethereal diazomethane until methylation was complete, and evaporated to dryness. The residue was worked up by c.c. (DCM – acetone, 7:0.5) to afford *1-(3-chloro-4--methoxy-5-nitro)-5-(2-methyltetrazol-5-ylmethyl)pyrrolidin-2-one* (**3n**) [0.40 g, 43.6%; found: $M^{+\cdot}$, 366.0832; $C_{14}H_{15}ClN_6O_4$ requires: $M^{+\cdot}$ 366.0843; ν_{max} (film) 1700, 1520, 1355 cm^{-1}; δ_H ($CDCl_3$)* 2.09m + 2.40m (4-H_2), 2.48m + 2.53m (3-H_2), 3.09+3.23 (2xdd; 14.8, 7.6 and 14.8, 3.8, respectively; 5-CH_2), 4.03s (OMe), 4.32s (*N*-Me), 4.70m (5-H), 7.856+7.863 (2xd, 2.7; 2'-H + 6'-H); *m/z* (relative intensity, 170°C) 366 (13; $M^{+\cdot}$), 269.0322 (100; M – CH_2CN_4Me; $C_{11}H_{10}ClN_2O_4$ requires: 269.0329), 222.0318 (10; 269 – HNO_2; $C_{11}H_9ClNO_2$ requires: 222.0322)] as an oil, and *1-(3-chloro-4-methoxy-5-nitro)-5--(1-methyltetrazol-5-ylmethyl)pyrrolidin-2-one* (**3m**) [0.15 g, 16.4%; m.p. 135-137°C; found: $M^{+\cdot}$, 366.0831; $C_{14}H_{15}ClN_6O_4$ requires: $M^{+\cdot}$, 366.0843; ν_{max} (KBr) 1705, 1525, 1360 cm^{-1}; δ_H ($CDCl_3$)* 2.05m (4-H_A), 2.5-2.75m (4-H_B + 3-H_2), 2.98+3.19 (2xdd; 15.6, 8.8 and 15.6, 3.5, respectively; 5-CH_2), 3.95s (*N*-Me), 4.01s (OMe), 4.92m (5-H), 7.84+7.87 (2xd; 2'-H + 6'-H); *m/z* (relative intensity; 170°C) 366 (13; $M^{+\cdot}$), 349 (10); 269 (100, M - CH_2CN_4Me), 222.0318 (14; 269 – HNO_2; $C_{11}H_9ClNO_2$ requires: 222.0322)] in the order of increasing polarities.

The *third part* of the reaction mixture was stirred with an aqueous solution of NaI (15 g) until compound **12** was consumed (*ca* 72 h) and extracted with ethyl acetate. The combined organic solutions were washed with 10% aqueous $NaHSO_3$ solution, dried and evaporated to dryness. The residue was worked up by c.c. (DCM – acetone, 7:3; then DCM – methanol, 7:1) to afford a crude product (2 g) which was dissolved in water (5 cm^3). When the solution was kept at 0°C, *1-(4-hydroxyphenyl)-5-(tetrazol-5-ylmethyl)pyrrolidin-2--one* (**3h**) [0.30 g, 46%; m.p. 265°C (dec.; recrystallizing at about 220°C); found: $M^{+\cdot}$, 259.1061; $C_{12}H_{13}N_5O_2$ requires: $M^{+\cdot}$ 259.1069; ν_{max} (KBr) 3300-2700 br, 1660 cm^{-1}; δ_H 2.01+2.26 (2xdddd; 12.9, 9.2, 5.6, 3.9 and 12.9, 9.0, 8.1, 7.9, respectively; 4-H_2), 2.40+2.44 (2xddd; 17.0, 9.0, 5.6 and 17.0, 9.2, 7.9, respectively; 3-H_2), 2.94+3.16 (2xdd; 14.2, 9.2 and 14.2, 3.5, respectively; 5-CH_2), 4.53dddd (9.2, 8.1, 3.9, 3.5; 5-H), 6.83+7.20 (AA'BB', 8.5; ArH's); *m/z* (relative intensity 200°C) 259 (29; $M^{+\cdot}$,) 216 (1.7; M - Ac), 176.0709 (100; $C_{10}H_{10}NO_2$ requires: 176.0712; M – CH_2CHN_4), 120 (6.9; $HC{\equiv}N^+C_6H_4OH$)] crystallized.

Reactions of compound **12** *with sodium chloride and sodium iodide*

(*a*) A mixture of compound **12** (0.18 g, 0.7 mmol), acetonitrile (10 cm^3), brine (10 cm^3) and conc. HCl (0.5 cm^3) was stirred at room temperature until, according to t.l.c., the starting compound was consumed (*ca* 30 h). Freshly prepared excess ethereal diazomethane solution was added and the mixture was stirred at room temperature until methylation was complete. The excess diazomethane was destroyed by adding acetic acid. The two phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic solutions were dried and evaporated to dryness. The residue was worked up by t.l.c. (DCM – methanol, 7:2, with a few drops of acetic acid added) to afford *1-(3-chloro-4-methoxyphenyl)-5-(2--methyltetrazol-5-ylmethyl)pyrrolidin-2-one* (**3l**) {0.12 g, 53%; found: $M^{+\cdot}$, 321.1001; $C_{14}H_{16}ClN_5O_2$ requires: $M^{+\cdot}$ 321.0993; ν_{max} (film) 1690 cm^{-1}; δ_H ($CDCl_3$)* 2.03+2.34 (2xdddd; 13.0, 8.5, 6.4, 4.2 and 13.0, 9.8, 8.0, 7.2, respectively; 4-H_2), 2.47+2.51 (2xddd; 17.0, 8.5, 7.2 and 17.0, 9.8, 6.4, respectively; 3-H_2), 2.99+3.19 (2xdd; 14.5, 8.2 and 14.5, 3.8, respectively; 5-CH_2), 3.91s (OMe), 4.31s (*N*-Me), 4.57 (dddd; 8.2, 8.0, 4.2, 3.8; 5-H), 6.96d (8.7; 5'-H), 7.30dd (8.7, 2.5; 6'-H), 7.45d (2.5; 2'-H); *m/z* (relative intensity, 170°C)

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

321 (21; $M^{+\cdot}$), 224 (100; M – CH_2CN_4Me), 189.0787 (4.2; 224 – Cl; $C_{11}H_{11}NO_2$ requires: 189.0790), 168 [5; a 10:1 doublet of $HC{\equiv}N^+C_6H_3Cl(OMe)$, 168.0222 ($C_8H_7ClNO$ requires: 168.0216) and $OCNC_6H_3ClO$, 167.9854 ($C_7H_3ClNO_2$ requires: 167.9852)], 147 (4.0; 189 – CH_2CO)} and *1-(3-chloro-4-methoxyphenyl)-5-(1-methyltetrazol-5-ylmethyl)pyrrolidin-2-one* (**3k**) {0.03 g, 13%; found: $M^{+\cdot}$, 321.0997; $C_{14}H_{16}ClN_5O_2$ requires: $M^{+\cdot}$ 321.0993; ν_{max} (film) 1690 cm^{-1}; δ_H* 2.06m (4-H_A), 2.48-2.68m (4-H_B + 3-H_2), 2.99+3.11 (2xdd; 15.6, 8.5 and 15.6, 3.8, respectively; 5-CH_2), 3.84 and 3.90s (2xs; OMe and *N*-Me, or inversely), 4.81m (5-H), 6.96d (8.8; 5'-H), 7.23dd (8.8, 2.5; 6'-H), 7.47d (2.5; 2'-H); *m/z* (relative intensity; 180°C) 321 (31; $M^{+\cdot}$), 237.0524 (17; M – CN_4Me – H; $C_{12}H_{12}ClNO_2$ requires 237.0557), 224 (100; M – CH_2CN_4Me), 189.0794 (5.5; 224 – Cl; $C_{11}H_{11}NO_2$ requires: 189.0790), 168 [6.9; a 8:1 doublet of $HC{\equiv}N^+C_6H_3Cl(OMe)$, 168.0222 ($C_8H_7ClNO$ requires: 168.0216) and $OCNC_6H_3ClO$, 167.9852 ($C_7H_3ClNO_2$ requires: 167.9852)], 147.0683 (9.1, 189 – CH_2CO; C_9H_9NO requires: 147.0684)} both as oils, in the order of increasing polarities.

(*b*) A mixture of compound **12** (0.1 g, 0.39 mmol), acetonitrile (7 cm^3), brine (7 cm^3) and conc. HCl (0.4 cm^3) was stirred at room temperature until, according to t.l.c. (DCM – acetone, 7:3), the starting compound was consumed (*ca* 3 h†). The mixture was extracted with ethyl acetate, the combined organic solutions were dried and evaporated to dryness. The residue was worked up by t.l.c. (solvent as above) to afford grey crystals of impure *1-(3-chloro-4-hydroxyphenyl)-5-(tetrazol-5-ylmethyl)pyrrolidin-2-one* (**3g**) [0.1 g, 87%; m.p. 235-240°C (turning white at about 160°C); found: $M^{+\cdot}$, 293.0675; $C_{12}H_{12}ClN_5O_2$ requires: 293.0680; ν_{max} (KBr) 3600-2800 v br, 1670 cm^{-1}; *m/z* (relative intensity; 220°C) 293 (3; M^+), 250 (24; M - Ac), 210 (100; M – CH_2CHN_4), 176.0704 ($C_{10}H_{10}NO$ requires: 176.0712; 210 – Cl + H); 154 (14; $HC{\equiv}N^+$-C_6H_3ClOH)].

When the reaction of compound **12** (0.05 g) with brine (5 cm^3) in acetonitrile (5 cm^3) was carried out in the *absence* of hydrochloric acid, the rate was extremely slow (*cf.* footnote†). After refluxing the mixture for 36 h only small amounts of compound **3g** were detected and identified by t.l.c.

(*c*) A mixture of compound **12** (0.1 g, 0.39 mmol), acetonitrile (7 cm^3), water (7 cm^3), sodium iodide (0.18 g, 1.2 mmol) and 5% H_2SO_4 (0.7 cm^3, 0.42 mmol) was stirred at room temperature until, according to t.l.c. (DCM – acetone, 7:3), compound **12** was consumed (*ca* 48 h). The mixture was neutralized (pH 5-6) by adding sodium acetate. Kieselgel G (2 g) was added and the mixture was evaporated to dryness. The residue was worked up by c.c. (20 g Kieselgel G; DCM – methanol, 7:2) to afford a somewhat impure sample of *1-(4-hydroxyphenyl)-5-(tetrazol-5-ylmethyl)pyrrolidin-2-one* (**3h**) [0.1 g, 99%; m.p. 198-203°C; ν_{max} (KBr) 3500-2700 v br, 1630 cm^{-1}] whose main component proved identical (IR, ^1H n.m.r.) with a pure sample of compound **3h** obtained without isolation of compound **12** by treating the reaction mixture obtained from compound **3a** and CAN with sodium iodide (see above).

Reaction of (methyltetrazolylmethyl)pyrrolidin-2-one **3e** *with CAN*

An aqueous solution (15 cm^3) of CAN (1.7 g, 3.1 mmol) was added dropwise to compound **3e** (0.30 g, 1.04 mmol) in acetonitrile (15 cm^3) with continuous stirring at -5°C. At this point the starting compound was

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

† The reaction of compound **12** with sodium chloride is catalyzed by HCl. The HCl concentration in (*b*) was significantly higher than in (*a*); therefore the reaction was considerably faster under the conditions described in (*b*) than under those described in (*a*).

consumed. The mixture was extracted with 1:1 (v/v) ethyl acetate – acetonitrile. The combined organic solutions were dried (Na_2CO_3) and evaporated to dryness. The residue was worked up by c.c. (DCM – acetone, 7:3) to afford *5-(2-methyltetrazol-5-ylmethyl)pyrrolidin-2-one* (**3f**) [0.16 g, 85%; found: $M^{+\cdot}$, 181.0960; $C_7H_{11}N_5O$ requires: $M^{+\cdot}$, 181.0964; ν_{max} (film) 3250 br, 1690 cm^{-1}; δ_H ($CDCl_3$) 1.93m (4-H_A), 2.32-2.44m (4-H_B + 3-H_2), 3.03+3.14 (2xdd; 15.0, 8.2 and 15.0, 4.8, respectively; 5-CH_2), 4.10m (5-H), 4.33s (*N*-Me), 6.50 br (NH); *m/z* (relative intensity; 150°C) 181 (4.5; $M^{+\cdot}$), 98.0594 (30; M – CN_4Me; C_5H_8NO requires: 98.0606), 84.0445 (100; M – CH_2CN_4Me; C_4H_6NO requires 84.0449)] as an oil.

(RS)-1-(4-Methoxyphenyl)-4-oxoazetidine-2-carbaldehyde (**15b**)

Trifluoroacetic anhydride (8.5 cm^3, 60 mmol) in dichloromethane (20 cm^3) was added dropwise to DMSO (5.7 cm^3, 81 mmol) in dichloromethane (30 cm^3) with continuous stirring at -60°C under argon. A crystalline product separated. Subsequently compound **15a**[7] (8.4 g, 40.5 mmol) in dichloromethane (80 cm^3) and, after 20 min., triethylamine (17.6 cm^3, 126 mmol) in dichloromethane (20 cm^3) were added to the suspension under the same conditions. The reaction mixture was allowed to warm up to room temperature, washed with water until neutral, dried and evaporated to dryness. The residue was taken up in ethyl acetate. The solution was washed with brine, dried and again evaporated to dryness. An aliquot (0.25 g) of the residue (7.3 g) was purified by t.l.c. (dichloromethane – acetone, 10:1) to afford the title compound (0.18 g, 64%) as an oil {found: $M^{+\cdot}$, 205.0729; $C_{11}H_{11}NO_3$ requires: $M^{+\cdot}$, 205.0739; ν_{max} (film) 1760-1720 br; δ_H ($CDCl_3$) 3.10+3.38 *ABX* (16.3, 2.7 and 6.0; 3-H_2), 4.40ddd (6.0, 2.7 and 4.4; 2-H), 9.72d (4.4; CHO); *m/z* (rel. intensity, %, 190°C) 205 (70; $M^{+\cdot}$), 176 (7.2; M - CHO), 163 (7.1; M - CH_2CO), 149.0478 ($C_8H_7NO_2$ requires: 149.0477; 10; OCN-PMF), 148.0762 (17; H_2C^+-CH=N-PMP; $C_9H_{10}NO$ requires: 148.0762), 134 [100; a 10:1 doublet of $HC{\equiv}N^+$-PMP (134.0602; C_8H_8NO requires: 134.0606) and 149 – Me (134.0238; $C_7H_4NO_2$ requires: 134.0242)]}.

The larger part of the crude product was converted into cyano derivative **15d** without further purification.

(RS)-4-Cyano-1-(4-methoxyphenyl)azetidin-2-one (**15d**)

(*i*) A mixture of crude carbaldehyde **15b** (7.1 g, containing 5.1 g, 25 mmol of the pure substance), hydroxyammonium chloride (2.9 g, 41.5 mmol), sodium acetate trihydrate (5.65 g, 4.15 mmol), dioxan (115 cm^3) and water (20 cm^3) was refluxed for 10 min. (t.l.c.: dichloromethane – acetone, 10:2), allowed to cool, diluted with dichloromethane, washed with water, dried and evaporated to dryness. An aliquot (0.26 g) of the residue (8.4 g) was purified by t.l.c. (dichloromethane – acetone, 10:2) to afford oxime **15c** {0.17 g, 99.5%; m.p. 106°C (from MeOH); found: $M^{+\cdot}$, 220.0838; $C_{11}H_{12}N_2O_3$ requires: 220.0848; ν_{max} (KBr) 3450, 1725 cm^{-1}; δ_H ($CDCl_3$; *ca* 89:11 *anti-syn* mixture; δ values of the *syn* isomer are in parentheses) 3.04 (2.98) + 3.40 (3.45) *ABX* (15.0, 2.5 and 5.5; 3-H_2), 4.65 (5.21) ddd (2.5, 5.5 and 8.0; 2-H), 7.49 (6.93) d (8.0; C*H*=N), 8.46 (8.88) br s (N-OH); *m/z* (rel. intensity; 190°C) 220 (71; $M^{+\cdot}$), 178 (15; M – CH_2CO), 161.0711 ($C_9H_9N_2O$ requires: 161.0715; 15; M – CH_2CO – OH), 149.0475 ($C_8H_7NO_2$ requires: 149.0477; 100; OCN-PMP), 134 [53; a 1:1 doublet of $HC{\equiv}N^+$-PMP (134.0602; C_8H_8NO requires: 134.0606) and 149 – Me (134.0236; $C_7H_4NO_2$ requires: 134.0242)], 123 (12; H_2N-PMP)}.

The larger part of crude oxime **15c** was converted into cyanoazetidinone **15d** without further purification.

(*ii*) Thus, crude oxime **15c** (8.15 g, containing 5.3 g, 24.2 mmol of the pure substance) was refluxed for 2 h with acetic anhydride (100 cm^3) (t.l.c. dichloromethane – acetone, 10:0.5). The mixture was evaporated to dryness and the residue was recrystallized from methanol to afford the title compound [3.4 g, 69.4%, overall; m.p. 115°C; found: C, 65.5; N, 13.75; $C_{11}H_{10}N_2O_2$ (202.2) requires: C, 65.3; N, 13.85%; ν_{max} (KBr) 2300w, 1760 cm^{-1}; δ_H ($CDCl_3$) 3.48+3.55 *ABX* (15.0, 2.8 and 5.5; 3-H_2), 4.57dd (2.8 and 5.5; 4-H)].

(RS)-1-(4-Methoxyphenyl)-4-(tetrazol-5-yl)azetidin-2-one (**2a**)

Anhydrous $AlCl_3$ (2.0 g, 14.8 mmol) was added to freshly dried THF (80 cm^3) in a dry flask with vigorous stirring. Stirring was continued for 10 min. NaN_3 (4.3 g, 66 mmol) was added and the mixture stirred for another 10 min. Compound **15d** (3.0 g, 14.8 mmol) was added. All these operations were carried out with ice-water cooling under argon. The reaction mixture was allowed to warm up to room temperature and then refluxed for 45 h (t.l.c. dichloromethane – acetone, 7:1) under argon, stirring being continued throughhout. The mixture was then evaporated to dryness. The residue was triturated with ice-water and the mixture acidified with conc. HCl. The crystalline product was filtered off and washed successively with 0.5N HCl, methanol and diethyl ether to afford the title compound {3.6 g, 99%; m.p. 170°C; $M^{+\cdot}$ 245.0882; $C_{11}H_{11}N_5O_2$ requires: $M^{+\cdot}$ 245.0913; ν_{max} (KBr) 3200-2950 br (with several local maxima), 1750 cm^{-1}; δ_H 3.36+3.71 *ABX* (14.8, 2.5 and 5.6; 3-H_2), 5.64dd (8.5 and 5.6; 4-H); *m/z* (rel. intensity, %; 180°C) 245 (100; $M^{+\cdot}$), 149.0475 ($C_8H_7NO_2$ requires: 149.0477; 98; OCN-PMF), 134 [66; a 1:1 doublet of $HC{\equiv}N^+$-PMP (134.0602; C_8H_8NO requires: 134.0606) and 149 – Me (134.0236; $C_7H_4NO_2$ requires: 134.0242)}.

Methyl (RS)-1-(4-methoxyphenyl-5-oxopyrrolidine-2-carboxylate (**16a**)

A mixture of dimethyl 2-bromopentanedioate[9] (4.62 g, 193 mmol), *p*-anisidine (47.4 g, 386 mmol) and diethyl ether (240 cm^3) was stirred for 90 h at room temperature. Part of the resulting *p*-anisidine hydrobromide crystallized and was filtered off after 40 and 90 h. The filtrate of the second fraction was evaporated to dryness. The residue was taken up in benzene (200 cm^3) and the mixture was refluxed for 27 h. A further amount of *p*-anisidine hydrobromide separated and was filtered off (total yield 39.5 g, 100%). The filtrate was washed with 1N HCl and water, dried, decolourized with charcoal and evaporated to dryness. The residue was crystallized twice from propan-2-ol to afford the first fraction of the title compound (9.0 g). The combined propan-2-olic filtrates were evaporated to dryness. The residue was worked up by c.c. (Kieselgel G, Merck; dichloromethane → dichloromethane – diethyl ether, 7:0.2) and the resulting product was recrystallized from propan-2-ol to afford a second fraction [10.8 g, total yield 41%; m.p. 88-89°C: found: C, 62.50; H, 6.15; N, 6.00; $C_{13}H_{15}NO_4$ (249.3) requires: C, 62.65; H, 6.05; N, 5.60; ν_{max} (KBr) 1735, 1695, 1250, 1210, 1025 cm^{-1}; δ_H ($CDCl_3$) 2.18m + 2.50m (3-H_2), 2.56m + 2.73m (4-H_2), 3.72s (CO_2Me), 4.66dd (8.6 and 3.00; 2-H)] of the title compound.

(RS)-5-Hydroxymethyl-1-(4-methoxyphenyl)pyrrolidin-2-one (**16b**)

$NaBH_4$ (6.04 g, 160 mmol) was added to an anhydrous methanolic (80 cm^3) solution of ester **16a** (19.8 g, 80 mmol) with continuous stirring and ice-water cooling. Stirring was continued for 17 h (t.l.c.:

dichloromethane – acetone, 7:3), with a further amount of $NaBH_4$ (3.02 g, 80 mmol) being added after 15 h. The mixture was acidified (pH 5) with conc. HCl and evaporated to dryness. The residue was taken up in dichloromethane and water, the two phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried and evaporated to dryness. The residue was purified by c.c. (Kieselgel G, Merck; dichloromethane - acetone, 7:3) to afford the title compound [16.8 g, 96%; found: C, 63.05; H, 6.2; $C_{12}H_{15}NO_3$ (221.25) requires: C, 63.15; H, 6.35%; ν_{max} (film) 3500 br, 1680 cm^{-1}; δ_H ($CDCl_3$) 2.05 br s (OH), 2.14+2.27 (12.7, 10.0, 5.7, 4.5, and 12.7, 10.0, 8.5, 7.0, respectively; 4-H_2), 2.51+2.66 (17.0, 5.7, 10.0, and 17.0, 7.0, 10.0, respectively; 3-H_2), 3.57+3.66 *ABX* (11.5, 4.0, and 11.5, 2.7, respectively, with further coupling, 3.0 and 5.0, respectively, to the OH group; 5-CH_2OH), 4.16dddd (8.5, 4.5, 4.0, 2.7; 5-H] as an oil.

(RS)-1-(4-Methoxyphenyl)-5-(methylsulfonyloxymethyl)pyrrolidin-2-one (**16c**)

Methanesulfonyl chloride (7.5 cm^3, 96 mmol) was dropwise added to a mixture of hydroxymethyl derivative **16b** (16.8 g, 76 mmol), pyridine (11.6 cm^3, 143 mmol) and dichloromethane (50 cm^3) with continuous stirring at 0°C. Stirring was continued for 4 h at room temperature (dichloromethane – acetone, 7:3) and the mixture was evaporated to dryness at *ca* 25 Pa, in order to remove most of the excess pyridine. The residue was taken up in dichloromethane and water and the mixture was neutralized by adding conc. HCl. The two phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried and evaporated to dryness. The residue was crystallized from ethanol to afford the title compound [13.2 g, 58%; m.p. 115°C (from ethanol); found: N, 4.75; S, 10.3; $C_{13}H_{17}NO_5S$ (299.3) requires: N, 4.7; S, 10.7%; ν_{max} (KBr) 1690, 1360, 1180 cm^{-1}; δ_H ($CDCl_3$) 2.14+2.41 (13.2, 10.0, 5.3, 4.0, and 13.2, 10.0, 8.6, 7.6, respectively; 4-H_2), 2.56+2.68 (17.2, 10.0, 5.3, and 17.2, 10.0, 7.6, respectively; 3-H_2), 2.90s (O_3SMe), 4.17+4.20 *ABX* (10.5, 4.1, 3.0; CH_2O), 4.38dddd (8.6, 4.1, 4.0, 3.0; 5-H)].

(RS)-5-Iodomethyl-1-(4-methoxyphenyl)pyrrolidin-2-one (**16d**)

A mixture of compound **16c** (13.2 g, 44 mmol), dry NaI (28.5 g, 190 mmol) and acetone (90 cm^3) was refluxed for 10 h and evaporated to dryness. The residue was thoroughly triturated with water to afford the title compound [13.3 g, 91%; m.p. 123°C; found: I, 37.85; N, 4.30; $C_{12}H_{14}INO_2$ (331.2) requires: I, 38.35; N, 4.25%; ν_{max} (KBr) 1690 cm^{-1}; δ_H ($CDCl_3$) 1.96+2.39 (13.2, 10.4, 5.8, 4.4, and 13.2, 10.5, 8.3, 6.5, respectively; 4-H_2); 2.54+2.73 (17.2, 10.5, 5.8, and 17.2, 10.4, 6.5, respectively; 3-H_2); 3.16+3.30 *ABX* (10.5, 6.3, 2.5; CH_2O), 4.11dddd (8.3, 6.3, 4.4, 2.5; 5-H].

(RS)-5-Cyanomethyl-1-(4-methoxyphenyl)pyrrolidin-2-one (**16e**)

A mixture of iodomethyl derivative **16d** (13.0 g, 39 mmol), NaCN (3.9 g, 79 mmol) and DMF (66 cm^3) was stirred for 30 h with ice-water cooling and poured into ice-water. The mixture was extracted with dichloromethane. The combined dichloromethane phases were washed with brine, dried and evaporated to dryness at *ca* 25 Pa. The residue was crystallized from ethanol to afford the title compound (2.8 g). The filtrate of this product was worked up by c.c. (Kieselgel 60 H, Merck; hexane – ethyl acetate, 7:3 → 1:1) and the appropriate fractions were combined and recrystallized from ethanol to afford a second fraction of the title

compound [0.9 g, total yield 41%; m.p. 103°C (from ethanol); found: C, 67.8; H, 6.2; N, 11.9; $C_{13}H_{14}N_2O_2$ (244.3) requires: C, 67.8; H, 6.15, N, 12.15; ν_{max} (KBr) 2275m, 1700 cm^{-1}; δ_H ($CDCl_3$) 2.10m + 2.52m (4-H_2), 2.53+2.59 *ABX* (16.7, 6.1, 3.5; CH_2CN), 2.61m + 2.76m (3-H_2), 4.34m (5-H)] as well as a more polar oily product (3.6 g) which, when dissolved in diethyl ether and kept for 24 at room temperature, afforded *N-(4-methoxyphenyl)-5-[1-(4-methoxyphenyl)-2-methyl-5-oxopyrrolidin-2-yl]-4-oxopentanamide* (**17b**) [3.3 g, 20%; m.p. 138-139°C; found: $M^{+\cdot}$, 424.1994; $C_{24}H_{28}N_2O_5$ requires: $M^{+\cdot}$, 424.1998; ν_{max} (KBr) 1715, 1660, 1645 cm^{-1}; δ_H ($CDCl_3$)* 1.34s (2'-Me), 2.10+2.34 (2xddd; 13.0, 9.5, 6.3 and 13.0, 10.0, 6.5, respectively; 3'-H_2), 2.55+2.63 (2xddd; 17.0, 9.5, 6.5 and 17.0, 10.0, 6.3, respectively; 4'-H_2), 2.5-2.62m (2-H_2), 2.6-2.75m (3-H_2), 2.66+2.68 (AB; 17.0; 5-H_2), 3.758+3.761 (2xs; 2xOMe), 6.78+7.31 and 6.87+6.99 (2xAA'BB'; 8.9; ArH's), 8.03 br (NH); NOE: 1.34 (2'-Me) → 6.99 (2"-H + 6"-H), 2.10 (3'-H_A), 2.67 (5-H_2); δ_C ($CDCl_3$)* 27.28 (2'-Me), 30.05 and 30.39 (C-4' and C-2, or inversely), 31.50 (C-3'), 38.82 (C-3), 50.86 (C-5), 55.37 and 55.40 (2xOMe), 63.02 (C-2'), 113.90+121.49 (C-2", C-6", C-3", C-5", NHAr), 114.65+130.54 (C-2", C-6", C-3", C-5", NAr), 128.21+131.28 (2xC-1"), 156.05+159.30 (2xC-4"), 169.75 (C-1), 175.78 (C-5'), 207.14 (C-4); *m/z* (rel. intensity; 170°C) 424 (28%; $M^{+\cdot}$), 204 (100; M – $CH_2COC_2H_4CONH$-PMF), 123 (18; H_2N-PMF), 108 (5.7; PhOMe)].

(RS)-1-(4-methoxyphenyl)-5-(tetrazol-5-ylmethyl)pyrrolidin-2-one (**3a**)

Anhydrous $AlCl_3$ (2.1 g, 15.6 mmol), NaN_3 (4.65 g, 71 mmol) and cyanomethyl compound **16e** (3.6 g, 15.6 mmol) were successively added at intervals of 10 min to dry THF (80 cm^3) with continuous stirring and ice-water cooling under nitrogen. The mixture was refluxed for 1 week and evaporated to dryness. The residue was triturated with water and the mixture was acidified with conc. HCl. The crystalline product was filtered off and washed successively with 1N HCl and dichloromethane to afford the crude title compound (3.1 g) which was recrystallized from methanol to afford the pure product {2.3 g, 54%; m.p. 203-204°C; found: C, 56.7; H, 5.75; $C_{13}H_{15}N_5O_2$ (273.3) requires: C, 57.1; H, 5.55%; ν_{max} (KBr) 3100-2600, 1650 cm^{-1}; δ_H 1.98+2.35 (12.8, 8.6, 6.5, 4.3, and 12.8, 8.4, 8.4, 8.0, respectively; 4-H_2), 2.48m (3-H_2), 2.99+3.18, *ABX* (14.6, 8.8 and 3.6; 5-CH_2), 4.60dddd (8.8, 8.0, 4.3 and 3.6; 5-H); *m/z* (relative intensity; 190°C), 273.1213 ($C_{13}H_{15}N_5O_2$ requires: 273.1226; 44; $M^{+\cdot}$), 230.1044 ($C_{11}H_{12}N_5O$ requires: 230.1042; 3.0; M – Ac), 190 (100; M – CH_2CHN_4), 149 (2.5; OCN-PMP), 148.0765 (3.4; H_2C^+-CH=N-PMP; $C_9H_{10}NO$ requires: 148.0762), 134 [6.4; a 1:4 doublet of HC≡N^+-PMP (134.0604; $C_8H_8N_2O$ requires: 134.0606) and 149 – Me (134.0236; $C_7H_4NO_2$ requires: 134.0242)], 122.0600 (C_7H_8NO requires: 122.0606; 6.2; HN-PMP)}.

Methylation of compound **3a** *with diazomethane*

Freshly prepared excess ethereal diazomethane solution was added to a suspension of compound **3a** (1.0 g, 3.6 mmol) in acetone (30 cm^3). The mixture was stirred at room temperature until, according to t.l.c. (DCM – methanol, 7:2), compound **3a** was consumed. The excess diazomethane was destroyed (acetic acid) and the mixture was evaporated to dryness. The residue was worked up by c.c. (DCM – acetone, 10:0.5) to afford *1-(4-methoxyphenyl)-5-(2-methyltetrazol-5-ylmethyl)pyrrolidin-2-one* (**3e**) {0.7 g, 68%; m.p. 79-80°C;

* Unprimed, primed and doubly primed locants refer to the ketoamide side chain, the pyrrolidine ring and the *N*-aryl substituents, respectively

found: $M^{+\cdot}$, 287.1370; $C_{14}H_{17}N_5O_2$ requires: $M^{+\cdot}$, 287.1382; ν_{max} (KBr) 1690 cm^{-1}; δ_H ($CDCl_3$) 2.02+2.33 (2xdddd; 13.0, 8.4, 7.0, 4.5 and 13.0, 9.8, 7.8, 7.5, respectively; 4-H_2), 2.49+2.51 (2xddd; 17.1, 8.4, 7.5 and 17.1, 9.8, 7.0, respectively; 3-H_2), 2.96+3.19 (2xdd; 14.6, 8.6 and 14.6, 3.6, respectively; 5-CH_2) 3.81s (OMe), 4.30s (*N*-Me), 4.56dddd (8.6, 7.8, 4.5, 3.6; 5-H); *m/z* (relative intensity; 190°C) 287 (25; $M^{+\cdot}$), 203 (1; M – CN_4Me – H, see below), 190 (100; M – CH_2CN_4Me), 148 (2.7; H_2C^+-CH=N-PMP), 134 [5.2; a 10:1 doublet of $HC{\equiv}N^+$-PMP (134.0604; C_8H_8NO requires: 134.0606) and $OCNC_6H_4O$ (134.0236; $C_7H_4NO_2$ requires: 134.0242)], 122.0600 (5.2; HN-PMP; C_7H_8NO requires: 122.0606)} and *1-(4-methoxyphenyl)-5-(1-methyltetrazol-5-ylmethyl)pyrrolidin-2-one* (**3c**) {0.31 g, 30%; m.p. 146-147°C; found: $M^{+\cdot}$, 287.1386; $C_{14}H_{17}N_5O_2$ requires: $M^{+\cdot}$, 287.1382; ν_{max} (KBr) 1680 cm^{-1}; δ_H ($CDCl_3$) 2.08m (4-H_A), 2.48-2.68m (4-H_A + 3-H_2), 2.94+3.08 (2xdd; 15.5, 8.3 and 15.5, 3.8, respectively; 5-CH_2), 3.74s (*N*-Me), 3.80s (OMe), 4.78m (5-H); NOE: 3.74 (*N*-Me) → 2.94+3.08 (5-CH_2), 7.23 (2'-H + 6'-H);* *m/z* (relative intensity; 180°C) 287 (31; $M^{+\cdot}$), 203.0958 (11; M – CN_4Me – H; $C_{12}H_{13}NO_2$ requires: 203.0946), 190 (100; M – CH_2CN_4Me), 148 (4.5; H_2C^+-CH=N-PMP), 134 [6.4; a 1:10 doublet of $HC{\equiv}N^+$-PMP (134.0601; C_8H_8NO requires: 134.0606) and $OCNC_6H_4O$, (134.0241; $C_7H_4NO_2$ requires: 134.0242)]} in increasing order of their polarities.

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