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Simple and Condensed β-Lactams. Part 20.[1] Reaction of Some 1-(4-Methoxyphenyl)azetidin-2-ones with Cerium(IV) Ammonium Nitrate (CAN): Trapping of the Quinone Imine Intermediate with Chloride and Iodide Anions

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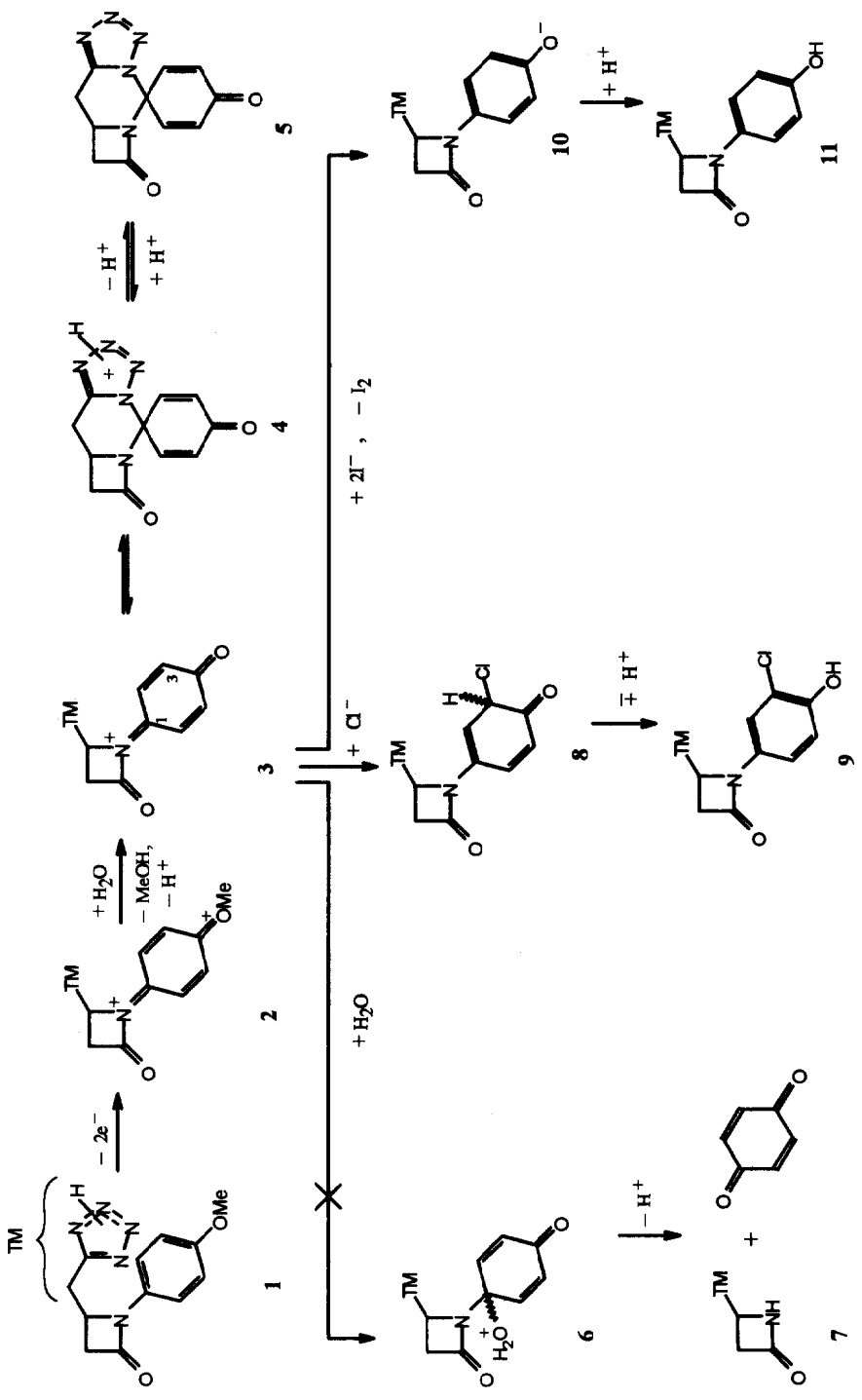
Key Words: β-Lactams; *N*-Deprotection; Quinone Imines; Trapping

Abstract: 1-(4-Methoxyphenyl)azetidin-2-ones **12** and **13**, when treated with cerium(IV) ammonium nitrate (CAN), afford either their *N*-deprotected derivatives (**19**, **26**) or the chlorinated compounds **22** and **27**, respectively, as the main products, depending on whether sodium chloride was present or not. A series of minor products (**20**, **21**, **23-25** and **29**, respectively) are formed in addition. 1-(4-Methoxyphenyl)azetidin-2-ones **13** and **14**, when treated successively with CAN and sodium iodide, afford the corresponding 1-(4-hydroxyphenyl)azetidin-2-ones **28** and **30**, respectively, in good yields. The latter reactions could possibly form the basis for elaboration of a potentially general method for dealkoxy-hydroxylation of *N*-(2- and 4-alkoxyphenyl)carboxamides. Mechanisms are suggested for the formation of compounds **19** - **30**.

N-Deprotection of 1-(4-methoxyphenyl)azetidin-2-ones by chemical oxidation with cerium(IV) ammonium nitrate (CAN)[2] or by anodic oxidation[3] is an established method in β-lactam chemistry. Anomalous behaviour of a 1-(4-methoxyphenyl)azetidin-2-one has been observed for the first time recently.[4] 1-(4-Methoxyphenyl)-4-(tetrazol-5-ylmethyl)azetidin-2-one (**1**), when treated with CAN under the usual conditions, does not yield the expected *N*-deprotected derivative **7**. Instead, when the reaction mixture was treated with sodium chloride or iodide before work-up, anomalous products: the chlorinated product **9** (in addition to several minor products) and the phenolic compound **11**, respectively, were obtained.[4]

This anomalous behaviour has been rationalized as shown in Scheme 1. In agreement with the generally accepted mechanism of *N*-de(4-methoxyphenylation),[3] quinone imine **3** was considered to be the key intermediate. At variance to the normal course of the reaction (attack of a water molecule at position 1 of the quinone imine moiety to yield adduct **6** and thence the *N*-deprotected derivative **7**), in the present case

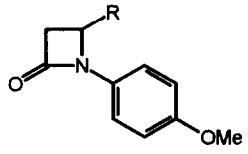


Scheme 1. Successive reaction of compound **1** with CAN and sodium chloride or iodide. Formation of chlorinated (**9**) and *O*-demethylated (**11**) products, respectively, rather than of the *N*-deprotected derivative **7**. All compounds are racemic; only one enantiomer is shown; TM = tetrazol-5-ylmethyl

intramolecular attack by a tetrazole nitrogen atom at the same position 1 has been assumed to take place. This would lead to the tetracyclic cation **4** and thence, by proton loss, to quinone aminal **5**, with the resulting triple equilibrium **3** ⇌ **4** ⇌ **5** being considerably shifted to the right. Formation of adduct **6** and thence of deprotected derivative **7** was, thus, assumed to be prevented because of rapid formation of quinone aminal **5** which may be regarded as a masked form of quinone imine **3**, stable to hydrolysis. On the other hand, added chloride anions do attack the quinone imine moiety of compound **3** at a different position, *viz.* at C-3. Formation of cyclohexadienone derivative **8** and thence of chlorinated product **9** is therefore not prevented. Nor is reduction of the quinone imine moiety by iodide ions prevented; this leads with subsequent proton uptake to phenolic compound **11**.[4]

In its final outcome all this amounts to trapping of quinone imine intermediate **3** by chloride ions and electrons, respectively. This raises the question whether intermediate formation of tetracyclic cation **4** and tetracyclic molecule **5** is indispensable for these trappings to occur; in other words whether type **3** quinone imines in which no interaction between the 4-substituent of the β-lactam ring and the quinone imine moiety is possible could also be trapped in a similar way. [The latter type quinone imines are of course those derived from 1-(4-methoxyphenyl)azetidin-2-ones which are prone to undergo *N*-deprotection by CAN under normal conditions.]

Here we report our studies into the reactions of 1-(4-methoxyphenyl)azetidin-2-ones **12-14** with CAN.



12 - 18 *

12[4]: R = CH_2O_3SMe
13: R = CONHBu
14: R = $CH_2CONHBu$
15[5]: R = CO_2Et
16: R = CO_2H
17: R = CO_2CO_2Et
18: R = $COCHN_2$

Compounds **13** and **14** were prepared starting with carboxylic acid **16**, itself obtained by alkaline hydrolysis of ester **15**.[5] Treatment of acid **16** with triphenylphosphine, CCl_4 and butylamine afforded carboxamide **13**, while acylation of diazomethane with mixed anhydride **17** (itself obtained by reaction of carboxylic acid **16** with ethyl chloroformate) and irradiation of the resulting diazoketone **18** in dichloromethane in the presence of butylamine furnished the homologous amide **14**.

Two types of oxidation experiments were carried out with the methylsulfonyloxymethyl derivative **12**: (i) with sodium chloride absent both during oxidation and work-up or with sodium chloride added before work-up, *i.e.* after oxidation was complete, and (ii) with the oxidation performed in the presence of added sodium chloride.† The results are shown in Tables 1 and 2, respectively.

When sodium chloride was absent both during oxidation and work-up (entries 1-5a, Table 1) the *N*-deprotected derivative **19**[6] was formed as the main product in agreement with expectation, dihydroxyphenyl

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* All compounds are racemic; only one enantiomer is shown

† In contrast to sodium iodide and bromide, sodium chloride has been found not to react with CAN under the conditions of our experiments

Table 1. Reaction of compound 12 with CAN in the absence of added NaCl[a]

	x[b] (h)	Method of work-up[c]	y[d] (min)	Products and yields[e] 19	20	21	22
1	0	*A1a*	-	24%	+[f]		
2	0	*A2a*	-	70%	+[f]		
3	0	*A1b*[g]	-	+[f]	+[f]	5.4%	
4	0	*A1a*[h]	-		14%[i]		
5a	0	*A2a*[j]	-	70%	+[f]		
5b		*B2a*[j]	45	+[f]		+[f]	76%
6	1.5	*B1a*	45	+[f]		+[f]	53%
7a	1[k]	*B2a*[j]	15	+[f]		+[f]	69%
7b		*B2a*[j]	45	+[f]		+[f]	55%
8	0	*B1b*	<2	19%	+[f]	+[f]	19%

[a] For a detailed description of the procedure, see Experimental

[b] Time of stirring after mixing of the reactants

[c] For the meaning of the symbols, see Experimental

[d] Time of stirring after addition of NaCl to the reaction mixture

[e] Non-optimized yields of isolated products

[f] Detected by t.l.c. (DC-Alufolien 60 PF_{254}, Merck; CH_2Cl_2-acetone, 7:3) in the filtrates of the crystalline product or products

[g] Without washing the combined EtOAc solutions with aq $NaHCO_3$ and aq $NaHSO_3$

[h] Twice the amounts of aq $NaHCO_3$, aq $NaHSO_3$ and water as stated in Experimental were used for washing the combined EtOAc solutions.In order to remove its dark colour, the dry residue was again dissolved in EtOAc, the solution treated with a second portion of aq $NaHSO_3$ and then worked up as usual

[i] The dry residue of the combined EtOAc solutions was dissolved in a small amount of CH_2Cl_2 rather than in EtOH in order to induce crystallization of the product

[j] The reaction mixture was divided into two equal parts and the two halves were separately worked up as indicated, using in both cases half the amounts of solvents and auxiliary reagents as stated in Experimental

[k] Cooling of the mixture was discontinued during this operation

Table 2. Reaction of compound 12 with CAN in the presence of added NaCl[a,b]

	m[c]	n[d]	x[e] (h)	Method of work-up[f]	y[g] (min)	Products and yields[h] 19	20	21	22	23	24
1	3	1	0	*B2a*	30	+[i]		+[i]	48%		
2a				*A2a*[j]	-	60%	+[i]		+[i]		
	3	1	0								
2b				*B2a*[j]	45	+[i]		+[i]	46%		
3	4.5	10	1	*A2b*	-	50%			1.2%	3%	8%
4	3+3[k]	10	1	*A2b*	-	50%			0.9%	3.6%	16%
5	6	10	0	*A2b*	-	45%			+[i]	4.5%	8.5%

[a] For a detailed description of the procedure, see Experimental

[b] In one experiment minute amounts of compound **25** were isolated (see text) in addition to the products shown in Table 2

[c] mol CAN/mol **12**

[d] mol NaCl/mol **12**

[e] Time of stirring after mixing of the reactans

[f] For the meaning of the symbols, see Experimental

[g] Time of stirring after addition of NaCl to the reaction mixture

[h] Non-optimized yields of isolated products

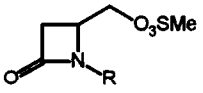
[i] Detected by t.l.c. (DC-Alufolien 60 PF_{254}, Merck; CH_2Cl_2-acetone, 7:3) in the filtrates of the crystalline product or products

[j] The reaction mixture was divided into two equal parts and the two halves were separately worked up as indicated, using in both cases half the amounts of solvents and auxiliary reagents as stated in Experimental

[k] The second portion of CAN was added after the reaction mixture had been stirred for x=1 h since, as shown by t.l.c. (see footnote i), compound **12** was not yet consumed at this point

derivative **20** being the by-product. In addition, nitro derivative **21** was obtained in one case. When, on the other hand, crystalline sodium chloride was added to the reaction mixture before work-up, until its aqueous phase became saturated (entries 5b-8), the chlorinated derivative **22** became the main product* in most cases (entries 5b-7), with the *N*-deprotected (**19**) and nitro derivatives (**21**), detected by t.l.c., as the by-products.

The initial oxidation product of compound **12** (obviously quinone imine analogue **32a** of compound **3**) is proved by the results of experiments 5a and 5b to be kinetically rather stable under the conditions of its



19 - 25†

19: R = H
20: R = $C_6H_3(OH)_2$ - (3,4)
21: R = $C_6H_3(OH)(NO_2)$ - (4,3)
22: R = $C_6H_3Cl(OH)$ - (3,4)
23: R = $C_6H_3Cl(OMe)$ - (3,4)
24: R = $C_6H_2Cl_2(OMe)$ - (3,5,4)
25: R = $C_6H_2Cl_2(OH)$ - (3,5,4)

formation. Depending on whether sodium chloride was added to the reaction mixture or not, the initial oxidation product went namely mainly to compound **22** (entry 5b) or compound **19** (entry 5a), respectively. Furthermore, when after completion of the oxidation, the reaction mixture was stirred for 1.5 h below 0 °C or for 1 h without cooling, considerable amounts of the initial oxidation product were still present since, on addition of sodium chloride, chlorinated derivative **22** was obtained as the main product (entries 6 and 7). These observations may, at the same time, be viewed as the experimental proof of the involvement of a quinone imine type intermediate in *N*-de(4-methoxyphenylations) of β-lactams.

Reaction of the quinone imine intermediate with chloride anions is not fast, either. When the oxidation mixture, after addition of crystalline sodium chloride, was namely shaken for just a few moments and the organic and aqueous phases were immediately separated, roughly equivalent amounts of the *N*-deprotected compound **19** (formed from the quinone imine without involvement of chloride anions) and of the chlorinated product **22** were obtained (entry 8).

When reaction of compound **12** with CAN was carried out in the presence of 1-10 mol-equivalents of sodium chloride (Table 2), the *N*-deprotected compound **19** was still the main product (entries 2a and 3 - 5), unless crystalline sodium chloride was added to the reaction mixture before work-up, until its aqueous phase became saturated (entries 1 and 2b). This again shows that reaction of the initial oxidation product (the quinone imine) with chloride ions is rather slow. In addition to the products already mentioned (**19-22**), two further compounds, the mono- (**23**) and dichloro*methoxy* derivative (**24**) were obtained when the oxidation was carried out in the presence of 10 mol-equivalents of sodium chloride (entries 3-5). In one case, minute amounts of the dichlorohydroxyphenyl derivative **25** were also isolated.

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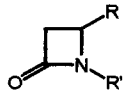
* Incorporation of chloride into the *N*-substituent of compound **12** under the conditions stated, rather than *N*-deprotection has been first noticed in preliminary experiments by E. Keskeny[7] in these laboratories.

† All compounds are racemic; only one enantiomer is shown

For a discussion of the mechanisms of formation of the novel type products **20-25**, see below.

In the course of these experiments it was occasionally noticed that 1:1 (v/v) acetonitrile - ethyl acetate mixtures serve much better than pure ethyl acetate for extraction of the *N*-deprotected compound **19** (compare entries 1 and 2, Table 1). Could we have failed to isolate compound **7** in our earlier studies[4] because of not having used acetonitrile - ethyl acetate mixtures for extraction? In order to settle this question, we have now tried to isolate compound **7** from oxidation mixtures of compound **1** by extraction with acetonitrile - ethyl acetate mixtures, but again without succes. The cases of compounds **1** and **12** therefore appear to be different.

Reaction of carboxamide **13** with CAN afforded the *N*-deprotected (**26**), the chlorinated (**27**) or the demethoxy-hydroxylation product **28**, depending on the conditions of work-up. Under the conditions of usual work-up (*i.e.* when the reaction mixture was not treated with either sodium chloride or sodium iodide), compound **26** was obtained. When the reaction mixture was, after consumption of the substrate, treated with crystalline sodium chloride, compound **27** resulted while similar treatment with crystalline sodium iodide led to compound **28** as the main product, accompained by minor amounts of compound **29**. An authentic sample of the latter was obtained by nitration of compound **28** with dilute nitric acid in aqueous acetonitrile, *i.e.* under conditions resembling those of the reaction of carboxamide **13** with CAN. Formation of



26 - 30*

	R	R'
26	CONHBu	H
27	CONHBu	$C_6H_3Cl(OH)$ - (3,4)
28	CONHBu	C_6H_4OH - (4)
29	CONHBu	$C_6H_3(OH)(NO_2)$ - (4,3)
30	$CH_2CONHBu$	C_6H_4OH - (4)

compounds **27** and **28** from **13** is analogous to the formation of compounds **9** and **11** from compound **1**, and of compound **22** from compound **12**; and indicates that the initial oxidation product of compound **13** (quinone imine **32b** analogous to compound **3**) is, similarly to the initial oxidation product of compound **12** (see above), kinetically comparatively stable under the conditions of its formation.

Reaction of compound **14** with CAN and treatment of the reaction mixture, after consumption of the substrate, with sodium iodide similarly afforded compound **30**. Demethoxy-hydroxylation of compounds **13** and **14** afford compounds **28** and **30**, respectively in good yields. These reactions could therefore form the basis for elaboration of a potentially general method for dealkoxy-hydroxylation of *N*-(2- and 4-alkoxyphenyl)carboxamides.

ON THE MECHANISMS OF FORMATION OF COMPOUNDS 19-30

N-Deprotected, chlorohydroxyphenyl and hydroxyphenyl derivatives (related to compounds **19** and **26**, **22** and **27**, and **28** and **30**, respectively) have, depending on the conditions used, been observed before among the products of reactions of 1-(4-methoxyphenyl)-azetidin-2-ones with CAN.[2-4] Formation of such products in the reactions discussed in the present paper may be rationalized by invoking the intermediacy of quinone imine

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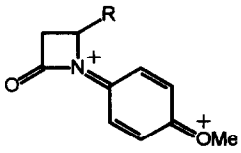
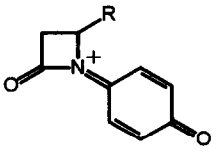
* All compounds are racemic; only one enantiomer is shown

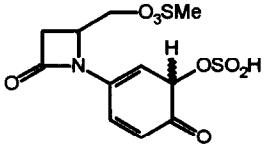
derivatives **31** and **32**, the latter being formed by demethoxy-hydroxylation of the former, accompained by proton loss [*cf.* transformations **3** → **7** (which, in the particular case when R = tetrazol-5-ylmethyl, does not take place), **3** → **9** and **3** → **11** shown in Scheme 1].



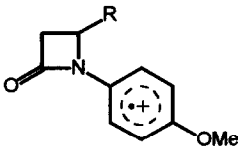
31 *



32 *



33 *



34 *

a: R = CH_2O_3SMe, **b**: R = CONHBu
c: R = $CH_2CONHBu$

All other products isolated in the course of the present study are of novel types.

Dihydroxyphenyl derivative **20** was obtained in 14% yield in the reaction of compound **12** with CAN when sodium chloride was neither present during the reaction, nor during work-up (Table 1, entry 4). This suggests that compound **20** is formed by reaction of quinone imine **32a** with hydrogen sulfite anions (added in the form of $NaHSO_3$ during work-up) to give adduct **33** which, by deprotonation - protonation and hydrolysis of the hydrogensulfite group, affords the final product. Thus, the reactions of hydrogen sulfite and chloride anions with quinone imine **32a** are assumed to be analogous which means that, if both anions are simultaneously present, they should compete for the quinone imine.

Formation of the chloro*methoxy*phenyl derivative **23** indicates that dication **31a** has two options in the presence of chloride anions: it may either react "normally" with water to afford quinone iminium cation **32a** or react with chloride anions to afford compound **35** and thence, by deprotonation, compound **23** (Scheme 2). Again we have competition of two nucleophiles (this time of water and chloride anions) for a quinone imine (**31a**). Consequently, the presence of large amounts of chloride anions in the reaction mixture in the course of the reaction should be favourable to the formation of compound **23**. This has indeed been found to be the case since compound **23** was present among the products only when the reaction of compound **12** and CAN was carried out in the presence of 10 mol-equivalents of sodium chloride (Table 2, entries 3-5).

Since 4.5-6 mol-equivalents of CAN were used in these reactions (instead of 2 mol-equivalents necessary for conversion of substrate **12** into quinone imine derivatives **31a** and **32a**) further oxidation of compound **23** could be expected. This would lead to the formation of quinone imine **36** (Scheme 2) which, similarly to its non-chlorinated analogue **31a**, could react either with chloride anions or with water to afford dichloromethoxy derivative **24** and quinone iminium cation **37**, respectively. Reaction of the latter with chloride anions, followed by deprotonation - protonation should then lead to dichlorohydroxyphenyl derivative **25**. In agreement with this picture, compounds **24** and **25** were obtained only in those experiments where compound **12** was allowed to react with excess CAN in the presence of large amounts of sodium chloride.

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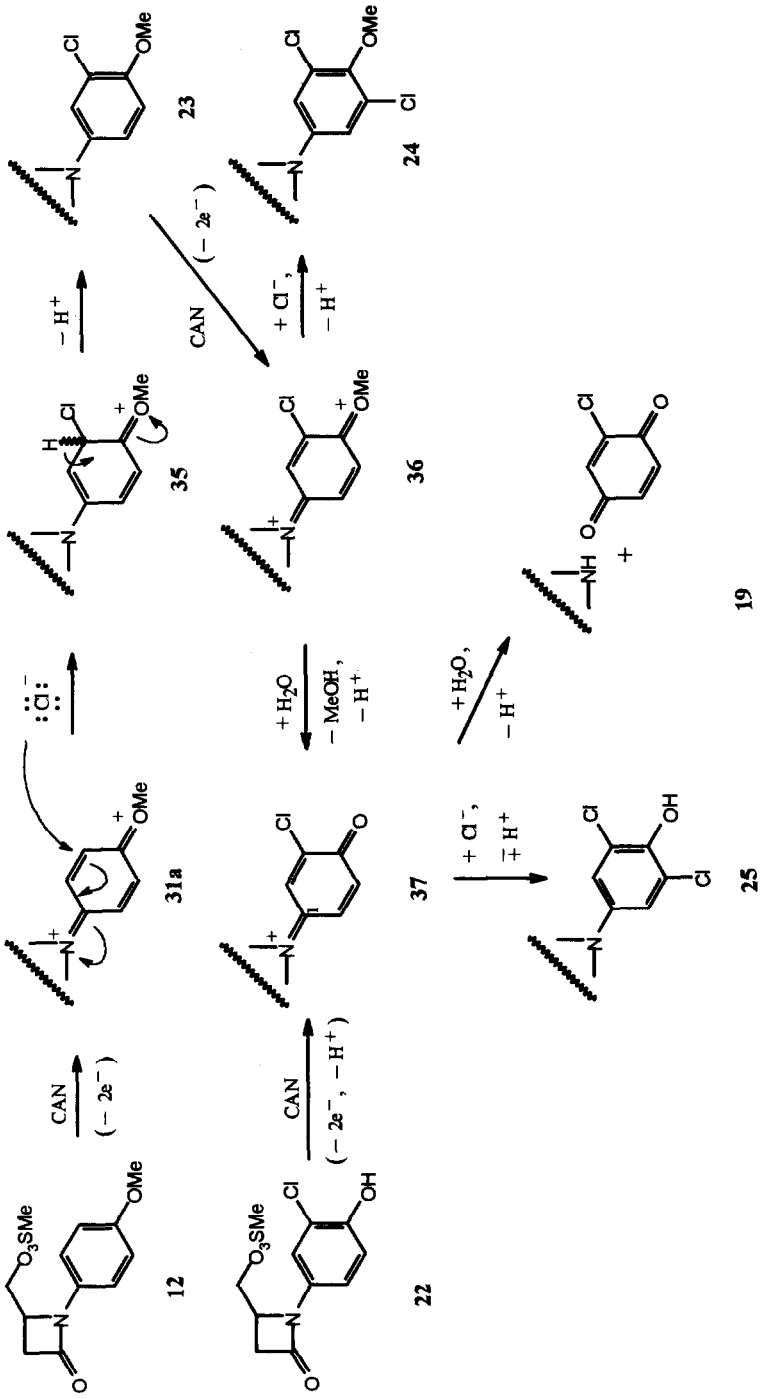
* Racemic compound; only one enantiomer is shown



Scheme 2. Mechanism of formation compounds 23-25 and alternative mechanism of formation of compound 19 in reactions of compound 12 and CAN carried out in the presence of sodium chloride. All compounds are racemic; only one enantiomer is shown.

Quinone imine **37** which could be formed also by oxidation of compound **22** by CAN should, similarly to its chlorine-free analogue **32a**, be able to react with water at position 1 of its quinone imine moiety which would lead to the deprotected derivative **19**. Operation of this alternative pathway of formation of compound **19** has been verified by treating compound **22** with CAN in the absence of sodium chloride in a separate experiment.

The structures of the nitro derivatives **29** and **21** suggest that these products might be formed by nitration of initially formed hydroxyphenyl derivative **28** and its 4-methylsulfonyloxymethyl analogue (which has not been isolated in our experiments), respectively. Indeed, treatment of compound **28** with dilute nitric acid in aqueous acetonitrile (*i.e.* under conditions similar to those of the reactions of compounds **12** and **13** with CAN) afforded compound **29** in good yield.

In order that nitro derivatives **29** and **21** may be actually formed *via* the S_E-Ar mechanism as tentatively assumed above, two conditions must be met: (*i*) formation of the corresponding hydroxyphenyl derivatives during the reaction or at some stage of the work-up procedure must be feasible and (*ii*) nitric acid should be present at this stage. Since nitric acid is formed as a co-product in oxidations by CAN, the second condition is automatically met, in any case before the organic products have been extracted from the aqueous acetonitrile solution.

Iodide and, to a lesser extent,[4] chloride anions are known to be able to reduce quinone imines to hydroxyphenyl derivatives. Therefore, in all cases but one, where nitro derivative **21** has been detected by t.l.c (Table 1, entries 5b-8, and Table 2, entries 1 and 2b) the corresponding hydroxyphenyl derivative could have been formed and been converted into compound **21** *via* the S_E-Ar pathway; the same pertains to the formation of nitro derivative **29**. However, in one case (Table 1, entry 3) nitro compound **21** was not only detected by t.l.c. but even isolated in 5.5% yield although no sodium chloride or iodide, nor any other auxiliary reagent was added which would have been able to reduce the intermediate quinone imine derivative **32a** to the hydroxyphenyl derivative. This suggests the existence of another pathway *via* which nitro derivatives **21** and **29** could be either formed exclusively or in addition to the competing S_E-Ar pathway. Whether the non-S_E-Ar pathway involves the intermediacy of radical species, *inter al.* of radical cations of type **34** (which are the one-electron oxidation products of compounds **12-14** and therefore the intermediates of the reactions leading to dications **31**) is not known.

EXPERIMENTAL

For column chromatographic (c.c.) separations Kieselgel G 60 (Merck) was used as the adsorbent. For identification of components of product mixtures and checking their purity thin layer chromatography (t.l.c.) on DC-Alufolien PF_{254} (Merck) was used in combination with IR spectroscopy. The individual compounds were detected by UV irradiation of the t.l.c. sheets 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 spectrometer (Zeiss, Jena). ^1H and ^{13}C NMR spectra were obtained, unless otherwise stated, with Varian XL-100 and XL-400 spectrometers in $CDCl_3$ at ca. 50°C, with TMS as the internal reference; J values are given in Hz. Mass spectra were obtained at 70eV with an AEI MS 902 instrument equipped with a direct insertion system.

Preparation of starting compounds **13** *and* **14**

(*a*) A mixture of compound **15**[5] (12.5 g, 50 mmol), methanol (60 cm^3), NaOH (2.2 g, 55 mmol) and water (140 cm^3) was stirred for 1/2 h at room temperature. The methanol was distilled off at reduced pressure. The residual aqueous solution was extracted with EtOAc (3x30 cm^3), acidified (pH 1) with cc. HCl and extracted with CH_2Cl_2 (3x40 cm^3). The combined CH_2Cl_2 phases were dried ($MgSO_4$) and evaporated to dryness at reduced pressure to give crude *1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylic acid* (**16**) [9.8 g, 89%; m.p. 159°C; ν_{max} (KBr) 1740, 1700 cm^{-1}].

(*b*) A mixture of crude carboxylic acid **16** (2.2 g, 10 mmol), acetonitrile (20 cm^3), Ph_3P (3.15 g, 12 mmol), butylamine (1.9 cm^3, 20 mmol) and CCl_4 (2 cm^3) was stirred for 1.5 h at room temperature. During this period the initial suspension turned gradually into a clear solution which was subsequently evaporated to dryness at reduced pressure. The residue was triturated with MeOH (10 cm^3) to give colourless crystals of *N-butyl-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxamide* (**13**) {1.9 g, 68%; m.p. 143°C; found C, 64.95; H, 7.45; N, 9.9; $C_{15}H_{20}N_2O_3$ (276.3) requires C, 65.2; H, 7.3; N, 10.15%; ν_{max} (KBr) 3250, 1725, 1630 cm^{-1};δ_H (400 MHz; $CDCl_3$) 0.87 [t, J=7.3 Hz; $NH(CH_2)_3CH_3$], 1.25[m; $NH(CH_2)_2CH_2CH_3$], 1.43(m; $NHCH_2CH_2CH_2CH_3$), 3.06+3.44(*AB*X, J_{gem}=−15.1, J_{vic}=2.7 and 6.0 Hz, respectively; 3-H_2), 3.28 (m; $NHCH_2$), 3.79 (s; OMe), 4.39 (dd, J=2.7 and 6.0 Hz; 2-H), 6.10(br t, J=5.7 Hz; NH), 6.88+7.28 (AA'BB', J=8.8 Hz; 4xAr-H)} which were filtered off and washed with diethyl ether.

(*c*) Triethylamine (6.6 cm^3, 47 mmol) and ethyl chloroformate (4.5 cm^3, 47 mmol) were added successively with continuous stirring and ice-cooling to a solution of crude acid **16** (9.8 g, 45 mmol) in anhydrous THF (140 cm^3). The mixture was cooled to -15°C and stirred for 20 min at this temperature. The crystalline triethylammonium salt was filtered off under argon. A freshly prepared ethereal (210 cm^3) diazomethane solution (140 mmol) was added to the filtrate and the mixture was allowed to warm up to room temperature with continuous stirring, whereby the desired *4-diazoacetyl-1-(4-methoxyphenyl)azetidin-2-one* (**18**) [5.6 g, 51%; m.p. 156°C (MeOH); found C, 58.5; H, 4.45; N, 17.4; $C_{12}H_{11}N_3O_3$ (245.2) requires C, 58.75; H, 4.5; N, 17.15%; ν_{max} (KBr) 2100, 1730/1720 cm^{-1}] gradually crystallized from the solution.

(*d*) A mixture of diazoketone **18** (1.3 g, 5.3 mmol), CH_2Cl_2 (140 cm^3) and butylamine (1.0 cm^3, 10 mmol) was irradiated with a high-pressure mercury immersion lamp (HPK 125, Philips) for 3.5 h at room temperature, and evaporated to dryness. The residue was worked up by c.c. at reduced pressure (2-2.6 kPa; CH_2Cl_2-acetone, 10:0.5 -10:1) to yield *N-butyl-[1-(4-methoxyphenyl)-4-oxoazetidin-2-yl]acetamide* (**14**) {0.6 g; 39%; m.p. 108°C (EtOAc - Et_2O); found C, 66.35; H, 7.45; N, 9.35; $C_{16}H_{22}N_2O_3$ (290.3) requires C, 66.2; H, 7.65; N, 9.65%; ν_{max} (KBr) 3300, 1740 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 0.90 [t, J=7.3 Hz; $NH(CH_2)_3CH_3$], 1.28 [m; $NH(CH_2)_2CH_2CH_3$], 1.41 (m; $NHCH_2CH_2CH_2CH_3$), 2.43+2.86 (*AB*X, J_{gem}=−14.5, J_{vic}=7.6 and 4.8 Hz, respectively; 2-CH_2) 2.84+3.30 (*AB*X, J_{gem}=−15.1, J_{vic}=2.4 and 5.3 Hz, respectively; 3-H_2), 3.20 (m; $NHCH_2$), 3.78 (s; OMe), 4.50 (dddd, J=7.6, 4.8, 5.3 and 2.4 Hz; 2-H), 5.73 (br t, J=5.7 Hz; NH), 6.86+7.29 (AA'BB', J=8.8 Hz; 4xAr-H)}.

Reactions of compound **12** *with CAN*

Method 1: in the absence of added NaCl (Table 1)

An aqueous (50 cm^3) solution of CAN (5.8 g, 10.5 mmol, 3 mol-equivalents) was added dropwise within 45 min to a solution of compound **12** (1.0 g, 3.5 mmol) in acetonitrile (40 cm^3) with continuous stirring at

-5 – 0°C. As shown by t.l.c. (CH_2Cl_2 - acetone, 7:3), compound **12** was consumed at this point. Stirring was continued at this temperature for 0-1.5 h and the mixture worked up according to one of the following methods.

(*A1*): EtOAc (40 cm^3) was added to the mixture and the aqueous phase extracted with EtOAc (3x50 cm^3). The combined organic phases were washed with saturated aq $NaHCO_3$ (10 cm^3), 10% aq $NaHSO_3$ (2x10 cm^3) and water (10 cm^3), dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The oily residue was (*a*) taken up in a small amount of ethanol whereupon the crystalline product gradually separated from the resulting solution or (*b*) worked up by c.c. at reduced pressure (2 - 2.5 kPa; CH_2Cl_2 - acetone, 10:0.1 → 10:0.5 → 7:1). The fraction containing the main product was crystallized as described in (*a*); all other fractions as well as the filtrates of the crystalline products were examined by t.l.c.

(*A2*): Same as (*A1*) except that a 1:1 (v/v) mixture of EtOAc and acetonitrile (3x50 cm^3) was used for extraction, and saturated aq Na_2CO_3 (10 cm^3) rather than aq $NaHCO_3$ for washing.

(*B1*) and (*B2*): EtOAc (40 cm^3) and crystalline NaCl were added until the aqueous phase became saturated. The mixture was stirred for 2 - 45 min at room temperature and then worked up as described in (*A1*) or (*A2*), respectively.

In two cases (entries 5 and 7) the reaction mixtures were divided into two equal parts and the two halves separately worked up by the methods indicated, using in all cases half the amounts of solvents and auxiliary reagents as stated above.

Method II: in the presence of added NaCl (Table 2)

An aqueos (15 cm^3/mmol CAN) solution of CAN (*m* mmol/mmol **12**) was added dropwise within 45 min to a solution of compound **12** (1.0 g, 3.5 mmol) in acetonitrile (40 cm^3) containing crystalline NaCl (*n* mmol/mmol **12**) with continuous stirring at -5 – 0°C. The salt gradually dissolved. Stirring was continued at this temperature for 0-1 h and the mixture worked up according to Method (*A2*) or (*B2*) described above.

In one case (entry 2) the reaction mixture was divided into two equal parts which were separately worked up by the methods indicated, using in both cases half the amounts of solvents and auxiliary reagents as stated above.

In addition to the known compound **19**[6] the following new compounds were obtained:

1-(3,4-Dihydroxyphenyl)-4-methylsulfonyloxymethylazetidin-2-one (**20**) [m.p. 124-125°C (CH_2Cl_2); found C, 46.25; H, 4.45; N, 5.0; $C_{11}H_{13}NO_6S$ (287.2) requires C, 46.0; H, 4.55; N, 4.9%; ν_{max} (KBr) 3530, 3200 br, 1740, 1360, 1170 cm^{-1}; δ_H (400 MHz; $CDCl_3$+DMSO-d_6)* 2.92 (s; OSO_2Me), 2.99+3.21 (*ABX*, J_{gem}=–14.9, J_{vic}=2.5 and 5.5 Hz, respectively; 3-H_2), 4.34 (dddd, J=2.5, 5.5, 3.6 and 4.1 Hz; 4-H), 4.49+4.55 (*ABX*, J_{gem}=–11.2, J_{vic}=3.6 and 4.1 Hz, respectively; CH_2O), 6.67 (dd, J=8.4 and 2.5 Hz, 6'-H), 6.81 (d, J=8.4 Hz; 5'-H), 7.05 (d, J=2.5 Hz; 2'-H), 7.69+8.33 (2xbr s; 2xOH)],

1-(4-Hydroxy-3-nitrophenyl)-4-methylsulfonyloxymethylazetidin-2-one (**21**) {m.p. 140-142°C (EtOH); found $M^{+\cdot}$ 316.0339; $C_{11}H_{12}N_2O_7S$ requires $M^{+\cdot}$ 316.0365; ν_{max} (KBr) 3380, 1750, 1520, 1330/1320 d, 1300, 1160 cm^{-1}; δ_H (400 MHz)* 3.07 (s; OSO_2Me), 3.03+3.35 (*ABX*, J_{gem}=–15.0, J_{vic}=2.5 and 5.5 Hz, respectively; 3-H_2), 4.45+4.66 (2xm; CH_2O), 4.47 (m; 4-H), 7.19 (d, J=8.6 Hz; 5'-H), 7.94 (dd, J=8.6 and 2.6 Hz; 6'-H), 7.97 (d, J=2.6 Hz; 2'-H), 10.40 (s; OH); δ_C (100 MHz) 37.95 (OSO_2Me), 39.84 (C3), 50.20 (C4), 67.00 (CH_2O), 111.48 (C5'), 121.25 (C2'), 127.83 (C6'), 130.34 (C1'), 133.03 (C3'), 151.89 (C4'),

* Primed locants refer to the aryl group

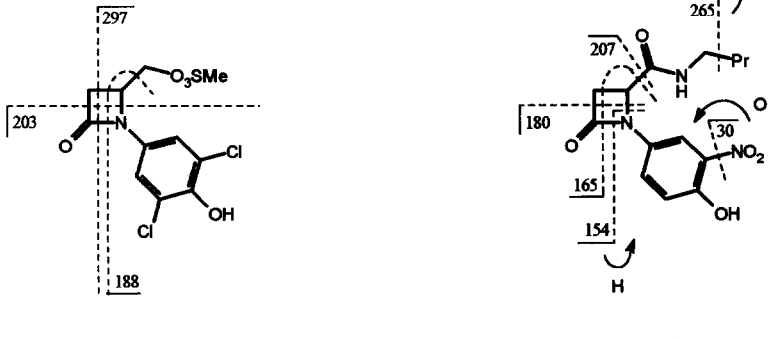
163.11 (C2); *m/z* (160°C; I%) 316 (47.9%; $M^{+\cdot}$), 274 (43.4%; M - CH_2CO), 238 (6%; M - O_2SMe + H), 220 (5.1%; M - O_3SMe - H), 207 (3.5%; M - CH_2O_3SMe), 195 (6.6%; M - $CHCH_2O_3SMe$ + H), 180 (24.3%; M - $CH_2CHCH_2O_3SMe$), 179 (4.7%), 178 (8.5%), 165 [*100*%; M - $NC_6H_3(OH)(NO_2)$ + H], 154 (7%), 133 (6.9%), 119 (7.5%), 110 (8.8%), 92 (5.4%; C_6H_4O), 79 (7.0%)},

1-(3-Chloro-4-hydroxyphenyl)-4-methylsulfonyloxymethyl-azetidin-2-one (**22**) [m.p. 178-181°C (EtOH); found C, 43.3; H, 4.05, Cl, 11.1; N, 5.1; $C_{11}H_{12}ClNO_5S$ (305.6) requires C, 43.2; H, 3.95; Cl, 11.6; N, 4.6%; ν_{max} (KBr) 3250, 1730, 1350, 1170 cm^{-1}; δ_H (400 MHz; $CDCl_3$+DMSO-d_6)* 3.00 (s; OSO_2Me), 3.00+3.25 (*ABX*, J_{gem}=−15.0, J_{vic}=2.5 and 5.5 Hz, respectively; 3-H_2), 4.43 (dddd, J=2.5, 5.5, 4.3 and 3.6 Hz; 4-H), 4.48+4.59 (*ABX*, J_{gem}=−11.3, J_{vic}=4.3 and 3.6 Hz, respectively; CH_2O), 6.96 (d, J=8.6 Hz; 5'-H), 7.14 (dd, J=8.6 and 2.5 Hz; 6'-H), 7.43 (d, J=2.5 Hz; 2'-H), 9.48 (s; O*H*)],

1-(3-Chloro-4-methoxyphenyl)-4-methylsulfonyloxymethylazetidin-2-one (**23**) [m.p. 145-146°C (EtOH); found C, 45.25; H, 4.15; Cl, 11.3; N, 4.1; $C_{12}H_{14}ClNO_5S$ (319.6) requires C, 45.05; H, 4.4; Cl, 11.1; N, 4.4%; ν_{max} (KBr) 1750, 1350, 1150 cm^{-1}; δ_H (100 MHz)* 2.99 (s; OSO_2Me), 3.01+3.27 (*ABX*, J_{gem}=−15.1, J_{vic}=2.4 and 5.3 Hz, respectively; 3-H_2), 3.89 (s; OMe), 4.28-4.70 (m; 4-H + CH_2O), 6.94 (d, J=8.6 Hz; 5'-H), 7.33 (dd, J=8.6 and 2.5 Hz; 6'-H), 7.48 (d, J=2.5 Hz; 2'-H)],

1-(3,5-Dichloro-4-methoxyphenyl)-4-methylsulfonyloxymethylazetidin-2-one (**24**) [m.p. 124-124.5°C (EtOH); found Cl, 20.0; N, 4.05; S, 9.0; $C_{12}H_{13}Cl_2NO_5S$ (354.2) requires Cl, 20.0; N, 3.95; S, 9.05%; ν_{max} (KBr) 1750, 1340, 1150 cm^{-1}; δ_H (400 MHz)* 3.05 (s; OSO_2Me), 3.03+3.32 (*ABX*, J_{gem}=−15.2, J_{vic}=2.5 and 5.6 Hz, respectively; 3-H_2), 3.87 (s; OMe), 4.41 (dddd, J=2.5, 5.6, 4.8 and 3.6 Hz; 4-H), 4.46+4.59 (*ABX*, J_{gem}=−11.0, J_{vic}=4.8 and 3.6 Hz, respectively; CH_2O), 7.40 (s; 2'-H+6'-H)].

In one experiment (oxidation according to Method II, method of work-up: *A2b*) minute amounts of a further compound were obtained which was sufficient only for obtaining the mass spectrum. The molecular mass (339), the relative intensities of the isotopic peaks and the main fragmentation pattern (Scheme 3) were in agreement with the structure of *1-(3,5-dichloro-4-hydroxyphenyl)-4-methylsulfonyloxymethylazetidin-2--one* (**25**)



25 **29**

Scheme 3. Main fragmentation modes of compounds **25** and **29**

* Primed locants refer to the aryl group

Successive reactions of compound **13** *with CAN, CAN and sodium chloride, and CAN and sodium iodide.*

(*a*) An aqueous solution (30 cm^3) of CAN (3.36 g, 6.1 mmol) was added dropwise within *ca.* 15 min to a solution of compound **13** (0.55 g, 2 mmol) in acetonitrile (25 cm^3) with continuous stirring at -10 – -5°C. [As shown by t.l.c. (CH_2Cl_2 - acetone, 10:0.5), compound **13** was consumed at this point.] The mixture was divided into two equal parts.

(*a1*) The first half of the reaction mixture was diluted with EtOAc (12 cm^3). The phases were separated and the aqueous phase was extracted with EtOAc (3x15 cm^3). The combined organic phases were washed with saturated aq Na_2CO_3 (3 cm^3), 10% aq $NaHSO_3$ (2x3 cm^3), saturated aq Na_2CO_3 (3 cm^3), and water (3 cm^3), dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The oily residue (0.18 g) was worked up by preparative t.l.c. (two 20x20 cm glass plates, coated with Kieselgel PF_{254}; CH_2Cl_2 - acetone, 7:3; elution: EtOH) to afford N-*butyl-(4-oxoazetidine-2-carboxamide)* (**26**) {0.07 g, 40%; m.p. 127-128°C (after trituration with diethyl ether); found C, 56.2; H, 8.3; N, 16.55; $C_8H_{14}N_2O_2$ (170.2) requires C, 56.45; H, 8.3; N, 16.45%; δ_H (400 MHz; $CDCl_3$+DMSO-d_6) 0.93 [t, J=7.2 Hz; $NH(CH_2)_3CH_3$], 1.35 [m; $NH(CH_2)_2CH_2CH_3$], 1.50 (m; $NHCH_2CH_2CH_2CH_3$), 2.96+3.29 (*AB*X, J_{gem}=–14.8, J_{vic}=2.6 and 5.8 Hz, respectively; 3-H_2), 3.25 (m; $NHCH_2$), 4.07 (dd, J=2.6 and 5.8 Hz; 2-H), 7.06 (br t, J=5.8 Hz; amide NH), 7.43 (br s; lactam NH)}.

(*a2*) The second half of the reaction mixture was diluted with EtOAc (12 cm^3). Crystalline sodium chloride (10 g) was added and the mixture stirred for 45 min at room temperature. The two phases were separated and the aqueous phase was extracted with a 1:1 (v/v) EtOAc - MeCN mixture (3x15 cm^3). The combined organic phases were washed, dried and evaporated to dryness as described in (*a1*). The oily residue (0.3 g) was crystallized from CH_2Cl_2 and then worked up by preparative t.l.c. as described in (*a1*) to give N-*butyl-[1-(3-chloro-4-hydroxyphenyl)-4-oxoazetidine-2-carboxamide]* (**27**) {0.12 g, 40%; m.p. 173–174°C (after trituration with diethyl ether); found Cl, 12.1; N, 9.25; $C_{14}H_{17}ClN_2O_3$ (296.8) requires Cl, 11.95; N, 9.45%; ν_{max} (KBr) 3340, 1730, 1650 cm^3; δ_H (400 MHz; $CDCl_3$+DMSO-d_6)* 0.90 [t, J=7.2 Hz; $NH(CH_2)_3CH_3$], 1.29 [m; $NH(CH_2)_2CH_2CH_3$], 1.47 (m; $NHCH_2CH_2CH_2CH_3$), 3.08+3.34 (*AB*X, J_{gem}=–14.7, J_{vic}=2.6 and 5.8 Hz, respectively; 3-H_2), 3.27 (m; $NHCH_2$), 4.38 (dd, J=2.6 and 5.8 Hz; 2-H), 6.94 (d, J=8.5 Hz; 5'-H), 6.98 (br t, J=5.8 Hz; 4-CONH), 7.19 (dd, J=8.5 and 2.5 Hz; 6'-H), 7.36 (d, J=2.5 Hz; 2'-H), 8.63 (br s; OH)].

(*b*) A solution of compound **13** (0.55 g, 2 mmol) was similarly treated with an aqueous solution of (30 cm^3) of CAN (2.75 g, 5.1 mmol). The mixture was saturated with crystalline NaI, stirred for 20 min at this temperature and extracted with EtOAc (5x25 cm^3). The combined organic phases were treated with crystalline $Na_2S_2O_5$ with continuous stirring, in order to remove the dark colour. The inorganic salts were filtered off and the filtrate was evapored to dryness at reduced pressure. The residue was worked up by c.c. (2 – 2.7 kPa; CH_2Cl_2-acetone, 10:1 → 10:1.5) to afford N-*butyl-[1-(4-hydroxy-3-nitrophenyl)-4--oxoazetidine-carboxamide]* (**29**) [20 mg, 3.2%] which proved identical (m.p., ^1H n.m.r.) with an authentic sample (see below), and N-*butyl-[1-(4-hydroxyphenyl)-4-oxoazetidine-2-carboxamide]* (**28**) {0.4 g, 76%; m.p. 175°C; found C, 64.5; H, 6.75; N, 10.9; $C_{14}H_{18}N_2O_3$ (262.3) requires C, 64.1; H, 6.9; N, 10.7%; δ_H (400 MHz; $CDCl_3$+DMSO-d_6) 0.89 [t, J=7.2 Hz; $NH(CH_2)_3CH_3$], 1.30 [m; $NH(CH_2)_2CH_2CH_3$], 1.46(m; $NHCH_2CH_2CH_2CH_3$), 3.04+3.27 (*AB*X, J_{gem}=–14.5, J_{vic}=2.5 and 5.5 Hz, respectively; 3-H_2), 3.24 (m;

* Primed locants refer to the aryl group

NHCH_2), 4.38 (dd, J=2.5 and 5.5 Hz; 2-H), 6.79+7.18 (AA'BB', J=8.6 Hz; 4xArH), 7.49 (br t, J=5.7 Hz; 4-CONH), 8.83 (s; -OH)}.

Successive reaction of compound **14** *with CAN and sodium iodide*

An aqueous solution (21 cm^3) of CAN (2.8 g, 5.1 mmol) was added within 15 min dropwise to a solution of compound **14** (0.5 g, 1.7 mmol) in acetonitrile (50 cm^3) with continuous stirring at -10 – -5 C. According to t.l.c. (CH_2Cl_2-acetone, 10:0.5), compound **14** was consumed at this point. Crystalline sodium iodide was added to the mixture at this temperature, until the aqueous phase became saturated. The mixture was then stirred for 20 min and extracted with EtOAc (5x30 cm^3). The combined organic phases were washed with 10% aq $NaHSO_3$, dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The residue (which still contained considerable amounts of NaI) was worked up by c.c. at reduced pressure (2-2.6 kPa; CH_2Cl_2-acetone, 10:0.5 → 10:1) to give *N-butyl-[1-(4-hydroxyphenyl)-4-oxoazetidin-2-yl]-acetamide* (**30**) {0.24 g, 50%; m.p. 125 C; found C, 65.4; H, 7.05; N, 10.3; $C_{15}H_{20}N_2O_3$ (276.3) requires C, 65.2; H, 7.3; N, 10.15%; ν_{max} (KBr) 3380, 1740, 1720sh, 1680 cm^{-1}; δ_H (400 MHz; $CDCl_3$+DMSO-d_6) 0.90 [t, J=7.2 Hz; NH$(CH_2)_3CH_3$], 1.30 [m; NH$(CH_2)_2CH_2CH_3$], 1.42 (m; NHC$H_2CH_2CH_2CH_3$), 2.37+2.93 (*ABX*, J_{gem}=−13.9, J_{vic}=8.5 and 4.6 Hz; respectively; 2-CH_2), 2.87+3.20 (*ABX*, J_{gem}=−14.9, J_{vic}=2.4 and 5.3 Hz, respectively; 3-H_2), 3.13 (m; NHCH_2), 4.39 (dddd, J=2.4, 5.3, 8.5 and 4.6 Hz; 2-H), 6.78+7.21 (AA'BB', J=8.6 Hz; 4xAr-H), 7.65 (br t, J=5.5 Hz; CONH), 9.00 (s; OH)}.

Nitration of compound **28**

A mixture of 65% HNO_3 (0.9 cm^3, 12 mmol) and water (8 cm^3) was added dropwise to a suspension of compound **28** (0.14 g, 0.53 mmol) in acetonitrile (7 cm^3) with continuous stirring at room temperature. A clear yellow solution formed gradually which became dark brown after *ca.* 20 min. Crystalline Na_2CO_3 (0.65 g) was added with ice -water cooling until the mixture became neutral. The mixture was then saturated with NaCl and extracted with EtOAc (5x7 cm^3). The combined EtOAc solutions were dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The dark brown residue was worked up by c.c. (2-2.6 kPa; CH_2Cl_2-acetone, 10:0.5) to afford the nitro compound **29** {0.10 g, 61%; m.p. 198 C (after trituration with diethyl ether); found $M^{+\cdot}$ 307.1243; $C_{14}H_{17}N_3O_5$ requires $M^{+\cdot}$ 307.1168; *m/z* (170 C; I%; *cf.* Scheme 3) 307 (43.1%; $M^{+\cdot}$), 277 (3.7%; M - NO), 265 (1.9%; M - C_3H_6), 207 (*100%*; M - CONHBu), 180 (10.8%; M - Ar*), 165 (60.2%; H_2C=NAr*), 161 (14.0), 154 (80.8%; NHAr*), 119 (9.7%), 98 (12.2%), 72 (11.7%), 57 (12.6%), 55 (12.6%); δ_H (400 MHz; $CDCl_3$+DMSO-d_6)† 0.91 [t, J=7.2 Hz; NH$(CH_2)_3CH_3$], 1.34 [m; NH$(CH_2)_2CH_2CH_3$], 1.50 (m; NHC$H_2CH_2CH_2CH_3$), 3.12+3.29 (*ABX*, J_{gem}=−14.6, J_{vic}=2.5 and 5.5 Hz, respectively; 3-H_2), 3.21+3.29 (m+m; NHCH_2), 4.57 (dd, J=2.5 and 5.5 Hz; 2-H), 7.12 (d, J=8.5 Hz; 5'-H), 7.76 (dd, J=8.5 and 2.5 Hz; 6'-H), 7.86 (d, J=2.5 Hz; 2'-H), 8.32 (br t, J=5.5 Hz; 4-CONH), 10.3 (br s; OH)}.

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* Ar = $C_6H_3(NO_2)OH$

† Primed locants refer to the aryl group

N-Deprotection of 1-(3-chloro-4-hydroxyphenyl)-4-methylsulfonyloxymethylazetidin-2-one **23** *by treatment with CAN*

An aqueous solution (25 cm^3) of CAN (2.9 g, 5.3 mmol) was added dropwise to a solution of compound **23** (0.53 g, 1.75 mmol) in acetonitrile (20 cm^3) with continuous stirring at -5°C. Compound **23** was consumed within *ca* 45 min. The mixture was worked up essentially according to Method *A2b* described above, except that preparative t.l.c. (20x20 cm glass plates, coated with Kieselgel PF_{254}; CH_2Cl_2-acetone, 7:3) rather than c.c. was used for purification of the product [0.16 g, 55%; m.p. 118-120°C] which proved identical (m.p. i.r., t.l.c.) with an authentic sample of compound **19**[6].

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