Reaction of Cerium(IV) Ammonium Nitrate with 3-Methylcephalosporins: Synthesis of a 2-Methoxy-3-methylcephalosporin

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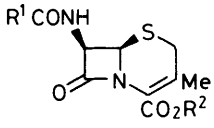
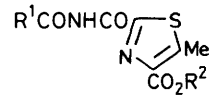
The cephalosporins (**1**)—(**3**) react with cerium(IV) ammonium nitrate (CAN) in aqueous acetic acid to give the thiazoles (**4**)—(**6**) respectively as the major products. The minor products from the reaction of the cephalosporin (**1**) with CAN in aqueous acetic acid were the esters (**7**), (**8**), (**10**), and (**11**). The cephalosporin (**1**) reacted with CAN in methanol under mild conditions to give a good yield of the 2-methoxy derivative (**13**). More vigorous conditions for the reaction of (**1**) and CAN in methanol gave a lower yield of the cephalosporin (**13**) and gave the esters (**4**), (**11**), (**14**), (**15**) and methyl phenylacetate as additional products. The mechanism involved in this oxidative rearrangement of the cephalosporins (**1**)—(**3**) is discussed.

In a continuation of the investigations by one of us into the chemistry of simple cephalosporins[1] we have studied the reactions of the β-lactams (**1**)—(**3**) with cerium(IV) ammonium nitrate (CAN).



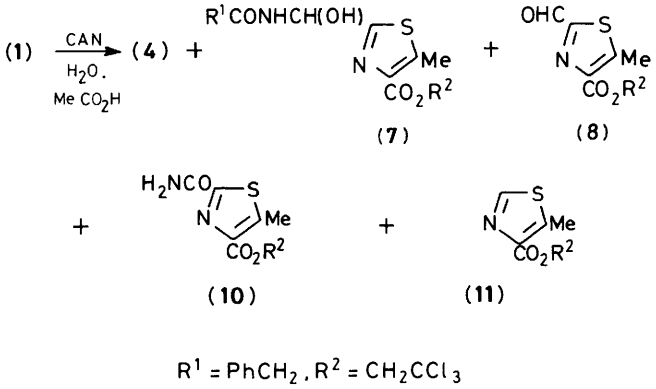


(**1**) $R^1 = PhCH_2$, $R^2 = CH_2CCl_3$ (**4**)
(**2**) $R^1 = PhOCH_2$, $R^2 = CH_2CCl_3$ (**5**)
(**3**) $R^1 = PhCH_2$, $R^2 = Me$ (**6**)

Treatment of the lactam (**1**) with an excess of CAN (10 equiv.) in aqueous acetic acid gave the crystalline thiazole (**4**) as the major product. The structure of this material was elucidated by spectroscopy and confirmed by *X*-ray analysis.[2] Similarly the cephalosporins (**2**) and (**3**) gave the thiazoles (**5**) and (**6**) under the same reaction conditions. In order to attempt to understand the mechanism of these remarkable transformations we undertook to study one of the reactions in more detail.

Careful chromatography of the crude product obtained from the oxidation of the lactam (**1**) with CAN (10 equiv.) in aqueous acetic acid led to the separation and identification of four minor products (Scheme 1). The crystalline hydroxy amide (**7**) was obtained in 7% yield. In an inert solvent, and with time, this compound gave phenylacetamide and the aldehyde (**8**). Treatment of (**7**) with a mixture of chloroform and ethanol containing a trace of acid gave the aldehyde (**8**) and the ethoxy amide (**9**) as expected. Interestingly the hydroxy amide (**7**) did not give the imide (**4**) on reaction with CAN (2 equiv.); prolonged reaction of (**7**) with the oxidising agent gave the aldehyde (**8**) (55% based on recovered starting material) as the only isolable product. The aldehyde (**8**), the amide (**10**), and the disubstituted thiazole (**11**) were all isolated in *ca.* 1% yield from the above reaction of the β-lactam (**1**) with CAN (10 equiv.). The amide (**10**) is derived by further reaction of the imide (**4**): in a separate experiment reaction of the imide (**4**) with CAN (2 equiv.) in aqueous acetic acid gave the amide (**10**) in 74% yield.

A reaction sequence for the oxidation of the β-lactam (**1**) with CAN in accord with the isolation of the products described

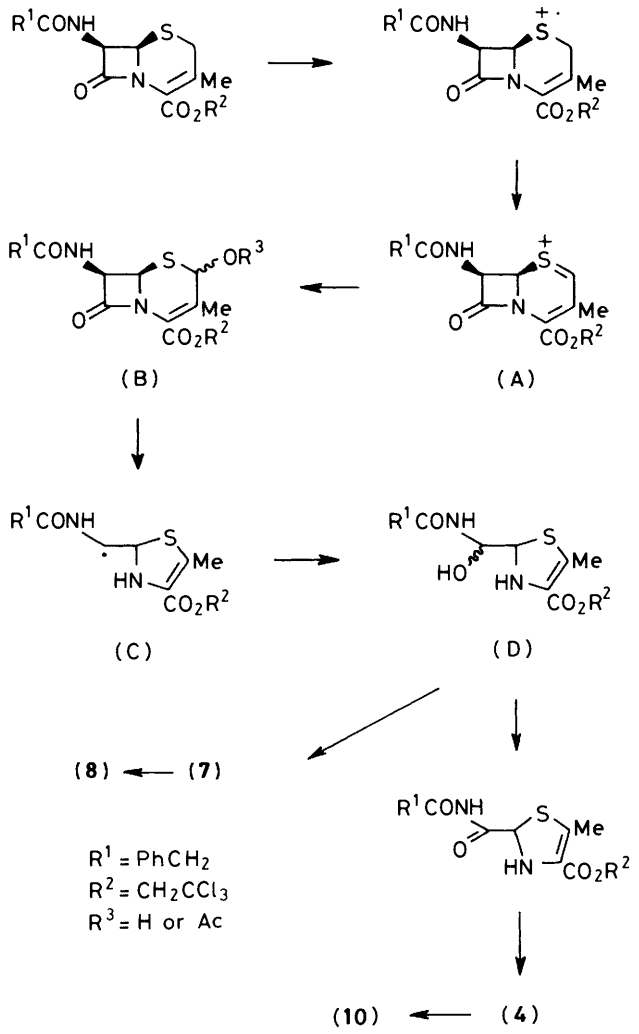


Scheme 1.

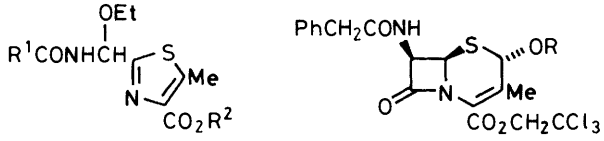
above is illustrated in Scheme 2. One-electron oxidation at the sulphur atom leads to the sulphur stabilized carbocation A after loss of a hydrogen atom. The carbocation would be trapped by the attendant nucleophiles to give the 2-hydroxy- or 2-acetoxy-cephalosporins B. Three processes must then take place: (*a*) ring contraction to give a five-membered ring containing nitrogen and sulphur; (*b*) oxidative removal of a one-carbon atom substituent from the five-membered ring. The carbon atom that is lost is the atom C-2 in the cephalosporin; (*c*) opening of the β-lactam ring presumably by initial loss of an electron from the oxygen atom of the β-lactam ring.

The order of the above events [*viz.* (*c*) relative to (*a*) and (*b*)] is not clear. There is precedent for some of the processes involved in this oxidative rearrangement, and these have been discussed previously.[2] The outcome of these changes is the formation of the radical (C). This radical could form the hydroxy amine (D) by way of an acyliminium ion. Oxidation of the side chain in (D) followed by aromatization of the five-membered ring would give the imide (**4**). Intermediate (D) can form the hydroxy amide (**7**) by direct aromatization.

As further evidence in favour of this sequence it was shown that the 2-acetoxycephalosporin (**12**) gave the imide (**4**) and hydroxy amide (**7**) as the major products on treatment with CAN (10 equiv.) in aqueous acetic acid. While the scale of this reaction did not allow the isolation of all the minor components from the reaction, the array of products on t.l.c. was very similar



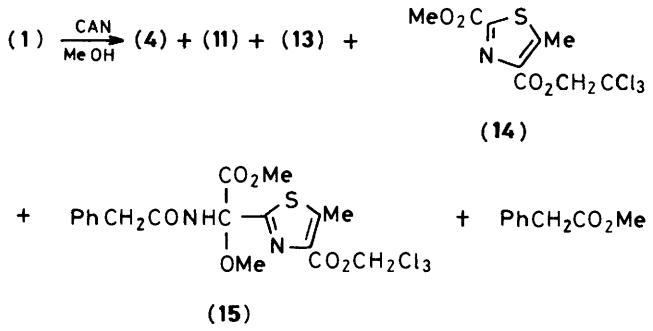
Scheme 2.



(9) $R^1 = PhCH_2$, $R^2 = CH_2CCl_3$ (12) R = Ac (13) R = Me

to that obtained from the corresponding 2-unsubstituted cephalosporin (**1**).

Having gained some confidence in the correctness of the initial steps in the mechanism of the transformation, we reasoned that the reaction could be employed to prepare useful 2-alkoxycephalosporins.[3] Our initial investigations have confirmed this postulate: thus reaction of the cephalosporin (**1**) with CAN (10 equiv.) in methanol gave a 50% yield of the 2-methoxy derivative (**13**). Reaction of the same cephalosporin with CAN in methanol under more vigorous conditions gave a range of products derived from more extensive oxidation of the substrate: the isolated and identified products included the imide (**4**), the disubstituted thiazole (**11**), the 2-methoxycephalosporin (**13**), the di-ester (**14**), the methoxy ester (**15**) and methyl phenylacetate (Scheme 3). The last three compounds were major components of the reaction mixture. Reaction of the



Scheme 3.

imide (**4**) with CAN in methanol gave the amide (**10**) as the major product together with a small amount of the ester (**14**).

In summary we have shown that the oxidation of a 3-methylcephalosporin with CAN can provide the 2-alkoxy derivative in good yield. Under different reaction conditions 3-methylcephalosporins are converted by CAN into the corresponding trisubstituted thiazole. Studies are continuing to ascertain the full versatility of this method of formation of 2-substituted cephalosporins, to comprehend the ring contraction process leading to the thiazole ring system, and to utilize the thiazoles for the synthesis of biologically interesting molecules.

Experimental

Unless stated otherwise the following procedures were adopted. M.p.s were obtained on an Electrothermal melting-point apparatus and are corrected. Optical rotations were measured at *ca.* +21 °C in $CHCl_3$ solution at 1.0% concentration. U.v. spectra were obtained in EtOH solution on a Pye Unicam SP-8200 spectrometer. I.r. spectra were recorded in $CHBr_3$ solution on Perkin-Elmer 177 and 257 spectrometers. ^1H N.m.r. spectra were obtained in $CDCl_3$ on a Varian XL-200 FT-nmr spectrometer. ^{13}C N.m.r. spectra were obtained in $CDCl_3$ on a JEOL FX-100 FT-nmr spectrometer. Accurate mass determinations were carried out on a Varian MAT 311A high-resolution mass spectrometer. Silica gel for column chromatography was Merck Kieselgel 60 (7734). Preparative t.l.c. was performed on Whatman PK6F silica gel plates. Ether corresponds to diethyl ether and light petroleum refers to the fraction b.p. 60—80 °C. Solutions in organic solvents were dried over anhydrous magnesium sulphate.

Reaction of (6R,7R)-2,2,2-*Trichloroethyl* 3-*Methyl*-7-*phenylacetamidoceph*-3-*em*-4-*carboxylate* (**1**) *with Cerium*(IV) *Ammonium Nitrate* (CAN).—(a) *In aqueous acetic acid.* 1M-CAN in 50% aqueous acetic acid (216 ml) was added over 0.5 h to a stirred solution of the ceph-3-em ester (**1**)[4] (10.0 g, 21.6 mmol) in glacial acetic acid (230 ml). The resulting yellow solution was stirred for a further 1 h and then diluted with water (2.5 l) and extracted with dichloromethane (4 × 0.5 l). The combined extracts were successively washed with water, 3.5% aqueous sodium hydrogen carbonate, and water (0.5 l each) and then dried and evaporated to a yellow foam (7.27 g) which was chromatographed on silica gel (400 g). Elution with ethyl acetate–light petroleum (1:1) gave a series of fractions (A)—(F). Fraction (A) (3.68 g) was subjected to further chromatography on silica gel (200 g) using dichloromethane–ether (19:1) as eluant to give 2,2,2-*trichloroethyl* 5-*methylthiazole*-4-*carboxylate* (**11**) as a colourless oil (68 mg), $\lambda_{max.}$ 230 (ε 4 910) and 270 nm (6 340); $\nu_{max.}$ 1 736, 1 238, and 788 cm^{-1}; δ_H 2.58 (3 H, s, Me), 5.03 (2 H, s, CH_2), and 8.38 (1 H, s, 2-H) [Found: M^+, 272.9185. $C_7H_6Cl_3NO_2S$ requires *M*, 272.9185]; 2,2,2-*trichloroethyl* 2-

formyl-5-methylthiazole-4-carboxylate (**8**) as a pale yellow oil (120 mg) which crystallised from ether–light petroleum (1:2) as colourless prisms (60 mg), m.p. 96—99 °C, $\lambda_{max.}$ 1 736, 1 692, and 776 cm^{-1}; δ_H 2.93 (3 H, s, Me), 5.05 (2 H, s, CH_2), and 9.98 (1 H, s, CHO) (Found: C, 31.7; H, 1.9; Cl 34.6; N, 4.6; S, 10.5. $C_8H_6Cl_3NO_3S$ requires C, 31.75; H, 2.0; Cl, 35.2; N, 4.6; S, 10.6%); and 2,2,2-*trichloroethyl* 5-*methyl*-2-*phenylacetamidocarbonylthiazole* 4-*carboxylate monohydrate* (**4**) as a yellow oil (2.06 g, 21.1%) which crystallised from ether (10 ml) as white prisms (1.47 g, 15.0%), m.p. 83—88 °C, $\lambda_{max.}$ 238 (ε 10 440) and 282 nm (10 030); $\nu_{max.}$ 3 340, 1 738, 1 702, 1 480, and 772 cm^{-1}; δ_H 2.89 (3 H, s, Me), 4.20 (2 H, s, $PhCH_2$), 5.00 (2 H, s, CH_2CCl_3), 7.2—7.4 (5 H, m, Ph), and 9.68 (1 H, s, NH); δ_C 14.4 (q, Me), 44.0 (t, $PhCH_2$), 74.6 (t, CH_2CCl_3), 94.5 (s, CCl_3), 127.3 (d, C-4′), 128.7 and 129.6 (two d, C-2′, C-6′ and C-3′, C-5′), 133.1 (s, C-1′), 141.2 (s, C-5), 153.7 (s, C-4), 157.0 and 157.6 (two s, CO·CN), 159.6 (s, CO_2), and 171.4 (s, CONH) [Found: C, 42.5; H, 3.3; Cl, 23.4; N, 6.2; S, 7.2. $C_{16}H_{13}Cl_3N_2O_4S{\cdot}H_2O$ requires C, 42.35; H, 3.3; Cl, 23.4; N, 6.2; S, 7.1%]. Fraction (B) (295 mg), a white solid m.p. 130—131 °C, was shown by t.l.c. to be a mixture of starting ceph-3-em ester (**1**) and the imide (**4**). Fraction (C) (244 mg) was purified further by preparative t.l.c. with dichloromethane–ether (19:1) as eluant to give 2,2,2-*trichloroethyl* 2-*aminocarbonyl*-5-*methylthiazole*-4-*carboxylate* (**10**) as a crystalline white solid (44 mg), m.p. 216—217 °C, $\lambda_{max.}$ 246.5 (ε 9 580) and 266infl nm (ε 8 100); $\nu_{max.}$ 3 510, 3 390, 1 738, 1 690, 1 572, and 774 cm^{-1}; δ_H 2.87 (3 H, s, Me), 5.00 (2 H, s, CH_2), 5.82 and 7.18 (2 H, br s, $CONH_2$); δ_C[$(CD_3)_2SO$], 15.2 (q, Me), 75.1 (t, CH_2CCl_3), 96.4 (s, CCl_3), 142.0 (s, C-5), 152.4 (s, C-4), and 160.8, 161.6, and 162.1 (3 s, CO_2, CN, and $CONH_2$) [Found: C, 30.4; H, 2.2; Cl, 33.4; N, 8.9; S, 9.9. $C_8H_7Cl_3N_2O_3S$ requires C, 30.25; H, 2.2; Cl, 33.5; N, 8.8; S, 10.1%]. Fraction (D) gave 2,2,2-*trichloroethyl* 2-[*hydroxy*(*phenylacetamido*)*methyl*]-5-*methylthiazole*-4-*carboxylate* (**7**) as a yellow foam (2.24 g, 23.7%) which crystallised from ether (20 ml) as white prisms (642 mg, 6.8%), m.p. 115—118 °C, $\lambda_{max.}$ 244 nm (ε 8 630); $\nu_{max.}$ 3 550, 3 420, 1 732, 1 670, 1 510, and 770 cm^{-1}; δ_H 2.80 (3 H, s, Me), 3.65 (2 H, s, $PhCH_2$), 4.94 and 5.06 (2 H, 2 × d, *J* 12 Hz, CH_2CCl_3), 5.42 (1 H, d, *J* 5 Hz, OH), 6.46 (1 H, t, *J* 5 Hz, CHOH), 7.2—7.6 (6 H, m, Ph and NH), δ_C 13.5 (q, Me), 43.0 (t, $PhCH_2$), 72.8 (d, CHOH), 74.2 (t, CH_2CCl_3), 94.5 (s, CCl_3), 127.1 (d, C-4′), 128.6 and 129.2 (two d, C-2′, C-6′ and C-3′, C-5′), 133.7 (s, C-1′), 139.3 (s, C-5), 147.9 (s, C-4), 160.0 (s, CO_2), 165.8 (s, CN), and 172.3 (s, CONH) [Found: C, 44.1; H, 3.6; Cl, 23.7; N, 6.4; S, 7.1. $C_{16}H_{15}Cl_3N_2O_4S$ requires C, 43.9; H, 3.45; Cl, 24.3; N, 6.4; S, 7.3%].

In other small scale (100—400 mg) experiments using the same reaction procedure 2,2,2-trichloroethyl (2*S*,6*R*,7*R*)-2-acetoxy-3-methyl-7-phenylacetamidoceph-3-em-4-carboxylate (**12**)[5] provided the *imide* (**4**) (15.7 %) and the *hydroxy amide* (**7**) (6.3%), 2,2,2-trichloroethyl (6*R*,7*R*)-3-methyl-7-phenoxyacetamidoceph-3-em-4-carboxylate (**2**)[4] gave 2,2,2-*trichloroethyl* 5-*methyl*-2-*phenoxyacetamidocarbonylthiazole*-4-*carboxylate* (**5**) (19.2%), m.p. 161—164 °C (from ethyl acetate), $\lambda_{max.}$ 272infl nm (ε 8 850), 277 (9 670), and 281infl nm (9 080) $\nu_{max.}$ 3 360, 1 768, 1 740, 1 710, and 1 476 cm^{-1}; δ_H 2.92 (3 H, s, Me), 4.91 (2 H, s, $PhOCH_2$), 5.03 (2 H, s, CH_2CCl_3), 6.9—7.4 (5 H, m, Ph), and 10.42 (1 H, br s, NH) [Found: C, 42.8; H, 2.9; Cl, 23.2; N, 6.3; S, 7.1. $C_{16}H_{13}Cl_3N_2O_5S$ requires C, 42.5; H, 2.9; Cl, 23.55; N, 6.2; S, 7.1%] and methyl (6*R*,7*R*)-3-methyl-7-phenylacetamidoceph-3-em-4-carboxylate[6] (**3**) gave *methyl* 5-*methyl*-2-*phenylacetamidocarbonylthiazole*-4-*carboxylate* (**6**) (27.7%), m.p. 147—147.5 °C (from ethyl acetate–ether), $\lambda_{max.}$ 285 nm (ε 10 380); $\nu_{max.}$ 3 350, 1 710, and 1 480 cm^{-1}; δ_H 2.81 (3 H, s, Me), 3.92 (3 H, s, CO_2Me), 4.22 (2 H, s, $PhCH_2$), 7.30 (5 H, s, Ph), and 9.60 (1 H, br s, NH) [Found: C, 56.8; H, 4.4; N, 8.65; S, 10.2. $C_{15}H_{14}N_2O_4S$ requires C, 56.6; H, 4.4; N, 8.8; S, 10.05%].

(b) *In methanol under mild conditions.* A solution of CAN (11.82 g, 21.6 mmol) in methanol (25 ml) was added to a stirred solution of the ceph-3-em ester (**1**) (1.00 g, 2.16 mmol) in tetrahydrofuran–methanol (1:2; 30 ml). The solution was stirred for 3.5 h, poured into iced water (250 ml) containing sodium metabisulphite (2.5 g), and extracted with dichloromethane (3 × 50 ml). The combined extracts were washed with 5% aqueous sodium hydrogen carbonate and water (50 ml each), dried, and evaporated to give a yellow oil (983 mg) which crystallised from ether (5 ml) to afford 2,2,2-*trichloroethyl* (2S,6R,7R)-2-*methoxy*-3-*methyl*-7-*phenylacetamidoceph*-3-*em*-4-*carboxylate* (**13**) as white prisms (450 mg, 43.2%), m.p. 134—135 °C (lit.,[5] 133.5—134 °C), $[\alpha]_D$ +128°, $\lambda_{max.}$ 267.5 nm (ε 8 810); $\nu_{max.}$ 3 410, 1 784, 1 742, 1 680, and 1 504 cm^{-1}; δ_H 2.20 (3 H, s, Me), 3.46 (3 H, s, OMe), 3.64 (2 H, s, $PhCH_2$), 4.76 (1 H, s, 2-H), 4.77 and 4.98 (2 H, 2 × d, *J* 12 Hz, CH_2CCl_3), 5.05 (1 H, d, *J* 5 Hz, 6-H), 5.88 (1 H, dd, *J* 9 and 5 Hz, 7-H), 6.26 (1 H, d, *J* 9 Hz, NH), 7.2—7.4 (5 H, m, Ph) [Found: C, 46.2; H, 3.9; Cl, 21.1; N, 5.6; S, 6.4. Calc. for $C_{19}H_{19}Cl_3N_2O_5S$: C, 46.2; H, 3.9; Cl, 21.5; N, 5.7; S, 6.5%]. The liquors were evaporated to give a yellow oil (433 mg), which was purified by preparative t.l.c. using dichloromethane–ether (19:1) to give additional (**13**) (78 mg, 8.1%).

(c) *In methanol under vigorous conditions.* 0.5M-CAN in methanol (432 ml) was added in one portion to a stirred solution of the ceph-3-em ester (**1**) (10.0 g, 21.6 mmol) in tetrahydrofuran (50 ml) and methanol (180 ml). The solution was stirred for 90 min and then evaporated to dryness under reduced pressure over a further 90 min. The residue was partitioned between ethyl acetate (0.25 l) and water (0.5 l) containing sodium metabisulphite (10 g). The layers were separated and the aqueous portion extracted with ethyl acetate (3 × 0.25 l). The combined organic extracts were washed with saturated brine solution (0.5 l), dried, and evaporated to give a red oil (10.0 g). This was chromotographed on silica gel (650 g) using ethyl acetate–light petroleum (b.p. 40—60 °C) (1:1) as eluant to give fractions (A)—(C). Fraction (A) [a mobile red oil (1.61 g)] was subjected to further chromatography on silica gel (60 g) with ethyl acetate–light petroleum (1:4) as eluant to give a colourless lachrymatory liquid (810 mg, 25.0%), identical by t.l.c., ^1H n.m.r. and i.r. spectroscopy to a sample of methyl phenylacetate, followed by a colourless oil (166 mg), which was shown by t.l.c. to be a mixture of methyl phenylacetate and the disubstituted thiazole (**11**). Fraction (B) [a viscous red oil (0.82 g)] was chromatographed further on silica gel (50 g) with ethyl acetate–light petroleum (1:2) as eluant to give 2,2,2-*trichloroethyl* 2-*methoxycarbonyl*-5-*methylthiazole*-4-*carboxylate* (**14**) as a colourless oil (582 mg, 8.1%), which crystallised from ether as colourless prisms, m.p. 116—118 °C, $\lambda_{max.}$ 1 740, 1 722, and 774 cm^{-1}; δ_H 2.90 (3 H, s, Me), 4.01 (3 H, s, CO_2Me), and 5.05 (2 H, s, CH_2); δ_C 13.8 (q, Me), 53.1 (q, OMe), 74.1 (t, CH_2CCl_3), 94.4 (s, CCl_3), 141.8 (s, C-5), 151.4 (s, C-4) and 154.0, 159.4, and 159.7 (3 s, CO_2Me, C=N, and $CO_2CH_2CCl_3$) [Found: C, 32.6; H, 2.5; Cl, 31.4; N, 4.4; S, 9.6. $C_9H_8Cl_3NO_4S$ requires C, 32.5; H, 2.4; Cl, 32.0; N, 4.2; S, 9.6%]; and the 2*S*-methoxyceph-3-em (**13**) as a pale brown gum (67 mg) which crystallised from ether to afford white prisms, m.p. 137—138 °C, $\lambda_{max.}$ 268 nm (ε 9 580), identical with the material described in (b) above. Fraction (C) [a yellow foam (1.79 g)] was chromatographed further on silica gel (80 g) using dichlormethane–ether (19:1) as eluant to give *methyl* α-*methoxy*-5-*methyl*-α-*phenylacetamido*-4-(2,2,2-*trichloroethoxycarbonylthiazol*-2-*ylacetate* (**15**) as a colourless viscous liquid (670 mg, 6.1%), which crystallised from ether as colourless prisms, m.p. 138—139 °C, $\lambda_{max.}$ 246 nm (ε 10 300); $\nu_{max.}$ 3 400, 1 748, 1 694, 1 490, and 772 cm^{-1}; δ_H 2.81 (3 H, s, Me), 3.21 (3 H, s, OMe), 3.67 (2 H, s, $PhCH_2$), 3.76 (3 H, s, CO_2Me), 4.95 and 5.01 (2 H, 2 × d, *J* 12 Hz, CH_2CCl_3), 7.2—7.4 (5 H, m, Ph), and 7.56 (1 H, br s, NH); δ_C 13.4 (g, CH_3), 43.3 (t, $PhCH_2$), 51.1 (q, OCH_3), 53.5 (q, CO_2CH_3), 74.1 (t, CH_2CCl_3), 85.2 (s, $COCH_3$), 94.4 (s, CCl_3), 126.9 (d, C-4′),

128.5 and 128.8 (two d, C-2′, C-6′ and C-3′, C-5′), 133.8 (s, C-1′), 139.0 (s, C-5), 148.4 (s, C-4), 159.6 ($CO_2CH_2CCl_3$), 163.0 and 166.8 (two s, C=N and CO_2CH_3), and 170.1 (s, CONH) [Found: C, 44.8; H, 3.75; Cl, 20.2; N, 5.5; S, 6.4. $C_{19}H_{19}Cl_3N_2O_6S$ requires C, 44.8; H, 3.8; Cl, 20.9; N, 5.5; S, 6.3%].

2,2,2-*Trichloroethyl* 2-*Formyl*-5-*methylthiazole*-4-*carboxylate* (**8**).—(a) *By acid-catalysed rearrangement of* (**7**). A solution of the hydroxy amide (**7**) (500 mg, 1.14 mmol) in chloroform (25 ml, containing ethanol) was stirred with Dowex AG 50W-X8 (100—200 mesh) ion-exchange resin (500 mg) for 3 days and filtered. The resin was washed with chloroform (25 ml). The filtrate was washed with 0.5M-hydrochloric acid, 3.5% aqueous sodium hydrogen carbonate and water (25 ml each) and then dried and evaporated to an oily solid (461 mg). This was chromatographed on silica gel (50 g) using dichloromethane–ether (19:1) as eluant to give the *aldehyde* (**8**) as a crystalline white solid (177 mg, 51.3%), m.p. 97—100 °C, with identical spectral properties to the material described above. Continued elution provided a pale yellow oil (167 mg) which crystallised from ether (2 ml) to afford 2,2,2-*trichloroethyl*-2-[*ethoxy*(*phenylacetamido*)*methyl*]-5-*methylthiazole*-4-*carboxylate* (**9**) (77 mg), m.p. 117—120 °C, $\lambda_{max.}$ 244.5 nm (ε 9 270), $\nu_{max.}$ 3 410, 1 730, 1 680, 1 490, and 768 cm^{-1}; δ_H 1.21 (3 H, t, *J* 7 Hz, CH_2Me), 2.78 (3 H, s, Me), 3.68 (2 H, s, $PhCH_2$), 3.75 (2 H, q, *J* 7 Hz, CH_2Me), 3.96 and 4.04 (2 H, 2 × d, *J* 12 Hz, CH_2CCl_3), 6.35 (1 H, d, *J* 8 Hz, CHOEt), 6.59 (1 H, d, *J* 8 Hz, NH), and 7.2—7.4 (5 H, m, Ph) [Found: C, 46.4; H, 4.1; Cl, 22.8; N, 6.0; S, 6.9. $C_{18}H_{19}Cl_3N_2O_4S$ requires C, 46.4; H, 4.1; Cl, 22.8; N, 6.0; S, 6.9%].

In $CDCl_3$ at room temperature the hydroxy amide (**7**) was converted into the aldehyde (**8**) and phenylacetamide over a period of 3 days.

(b) *From attempted further oxidation of* (**7**) *with cerium*(IV) *ammonium nitrate* (CAN). 1M-CAN in 50% aqueous acetic acid (1.5 ml) was added to a stirred solution of the hydroxy amide (**7**) (328 mg, 0.75 mmol) in glacial acetic acid (9 ml). The solution was stirred for 23 h and then diluted with water (100 ml) and extracted with dichloromethane (4 × 20 ml). The combined extracts were washed with water, 3.5% aqueous sodium hydrogen carbonate, and water (40 ml each), dried, and evaporated to give a crystalline solid (264 mg). Preparative t.l.c. using ethyl acetate–light petroleum (1:1) as eluant gave the unchanged hydroxy amide (**7**) (58 mg) and *aldehyde* (**8**) (103 mg), identical in all respects with the material described above.

2,2,2-*Trichloroethyl* 2-*Aminocarbonyl*-5-*methylthiazole*-4-*carboxylate* (**10**).—A solution of CAN (2.52 g, 4.6 mmol) in methanol (10 ml) was added to a stirred solution of the imide monohydrate (**4**) (1.00 g, 2.2 mmol) in tetrahydrofuran (5 ml) and methanol (20 ml). After *ca.* 40 min a solid started to precipitate and after 2 h the mixture was refrigerated for 1 h; the crystalline precipitate was filtered off, washed with cold methanol (10 ml), and dried to give the *amide* (**10**) (311 mg, 44.5%), m.p. 216—217 °C, $\lambda_{max.}$ 248.5 nm (ε 8 300) and 266infl nm (7 140). The combined filtrate and washings were partitioned between cold 1% aqueous sodium metabisulphite (250 ml) and chloroform (50 ml). The layers were separated and the aqueous portion extracted with chloroform (2 × 50 ml). The combined extracts were washed with 5% aqueous sodium hydrogen carbonate and water (50 ml each), dried, and evaporated to give an oily white solid (681 mg) which was stirred with ether (5 ml) to give additional *amide* (**10**) (294 mg, 42.1%), m.p. 218—219 °C, $\lambda_{max.}$ 248 (ε 8 520) and 265infl nm (7 270). Both crops of (**10**) were identical (i.r. and ^1H n.m.r.) to the authentic material described above. Purification of the liquor material by preparative t.l.c. (using ethyl acetate–light petroleum (1:1) as eluant gave further *amide* (**10**) (16 mg, 2.3%) and crystalline diester (**14**) (54 mg, 7.4%), m.p. 114—116 °C, $\lambda_{max.}$ 246.5 (ε 6 450) and 275 nm (ε 7 050), identical with authentic (**14**) described above.

Similar treatment of the imide (**4**) in glacial acetic acid with 1M-CAN in 50% aqueous acetic acid (2.0 equiv.) for 30 h gave the *amide* (**10**) in 74.4% yield.

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