Novel Alkoxylations of Cephalosporins by Cerium(IV) Salts and by Electro-oxidative Procedures

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Electrolyses of cephalosporins in methanol–tetrahydrofuran mixtures in the presence of tetraethylammonium tosylate provide useful syntheses of the corresponding 2-methoxy derivatives [(**2**), (**3b**), and (**6**)]. The same derivatives are produced when the cephalosporins are treated with cerium(IV) ammonium nitrate (CAN) in methanolic tetrahydrofuran. Alkoxylations of the cephalosporin (**1**) by CAN or by the electro-oxidative procedure, in the presence of ethanol, propan-2-ol, or benzyl alcohol, lead to the corresponding 2-ethoxy (**7a**), 2-isopropoxy (**7b**), and 2-benzyloxy derivatives.

Oxidations of organic molecules resulting in cleavage of C–H bonds and the production of more functionalised molecules can be carried out with a range of reagents when the C–H bond is activated by a suitably positioned α-substituent (*i.e.* a CC multiple bond or a heteroatom). In connection with studies on the chemistry of cephalosporins,[1] we required a convenient and high yielding procedure for the synthesis of 2-alkoxy derivatives directly from the parent cephalosporins.[2] Existing methods are lengthy or low yielding, or both.[3] In this paper we show that 2-alkoxy cephalosporins can be prepared directly and in one step from the parent cephalosporin, by alkoxylation in the presence of cerium(IV) ammonium nitrate (CAN)[4] or by an electro-oxidative procedure.

We first examined the electrochemical oxidation of the cephalosporin (**1**). When a solution of (**1**)[5] in 3:1 methanol–tetrahydrofuran was electrolysed at +1.1 V in the presence of tetraethylammonium tosylate (the reaction was monitored by chromatography), the cephalosporin was converted almost quantitatively into a single product within 2.5 h. Work-up and chromatography then gave the corresponding, known 2-methoxy derivative (**2**)[6] in 67% yield. The 2-methoxycephalosporin (**2**) was also produced (54%) when (**1**) was treated with 10 equiv. of the cerium(IV) salt [ceric ammonium nitrate (CAN)[7]] in methanolic tetrahydrofuran at 25 °C for 3.5 h.

In a similar manner, electrolysis of the cephalosporin (**3a**)[8] containing a trichloroethyl ester group, in methanol–tetrahydrofuran led to the 2-methoxy derivative (**3b**) (40%)[9] which was also produced, in similar yield, when the cephalosporin (**3a**) was treated with CAN.[10] Interestingly we obtained no evidence for the co-formation of thiazole products [*viz.* (**4**)] during the electrochemical oxidation or the treatment of (**3a**) with CAN. Thiazoles of type (**4**) have previously been shown to be major products when some cephalosporins are treated with CAN in aqueous acidic media.[10]

The versatility of these direct and complementary procedures for the methoxylation of cephalosporins, based on electrochemistry and cerium(IV) salts, was fully demonstrated when a number of alternatively substituted cephalosporins were examined [(**5**) ⟶ (**6**)]. It was interesting that in addition to 'methoxylation,' oxidation of (**1**) in the presence of ethanol, propan-2-ol, or benzyl alcohol, led to the corresponding 2-ethoxy (**7a**), 2-isopropoxy (**7b**), and 2-benzyloxy (**7c**) derivatives in acceptable yields. However, attempts to extend the oxidation procedures to the more acid-labile cephalosporins (**8**) incorporating furan and thiophene moieties in their structures were unsuccessful.

The direct alkoxylations of cephalosporins to the corresponding 2-alkoxy derivatives can thus be achieved in a complementary manner by anodic oxidation or by treatment with CAN, in the presence of alcoholic solvents. Both oxidation procedures no doubt proceed *via* one-electron transfer processes involving the sulphur atoms, and possibly the CC double bonds of the cephalosporins, ultimately leading to the stabilised carbocation intermediate (**9**). Significantly, under the reaction conditions, no other products were detected resulting from oxidation at sulphur or from cleavage of the CS bond, or from additions to the 3,4-double bonds in any of the oxidations of the cephalosporins.[11]

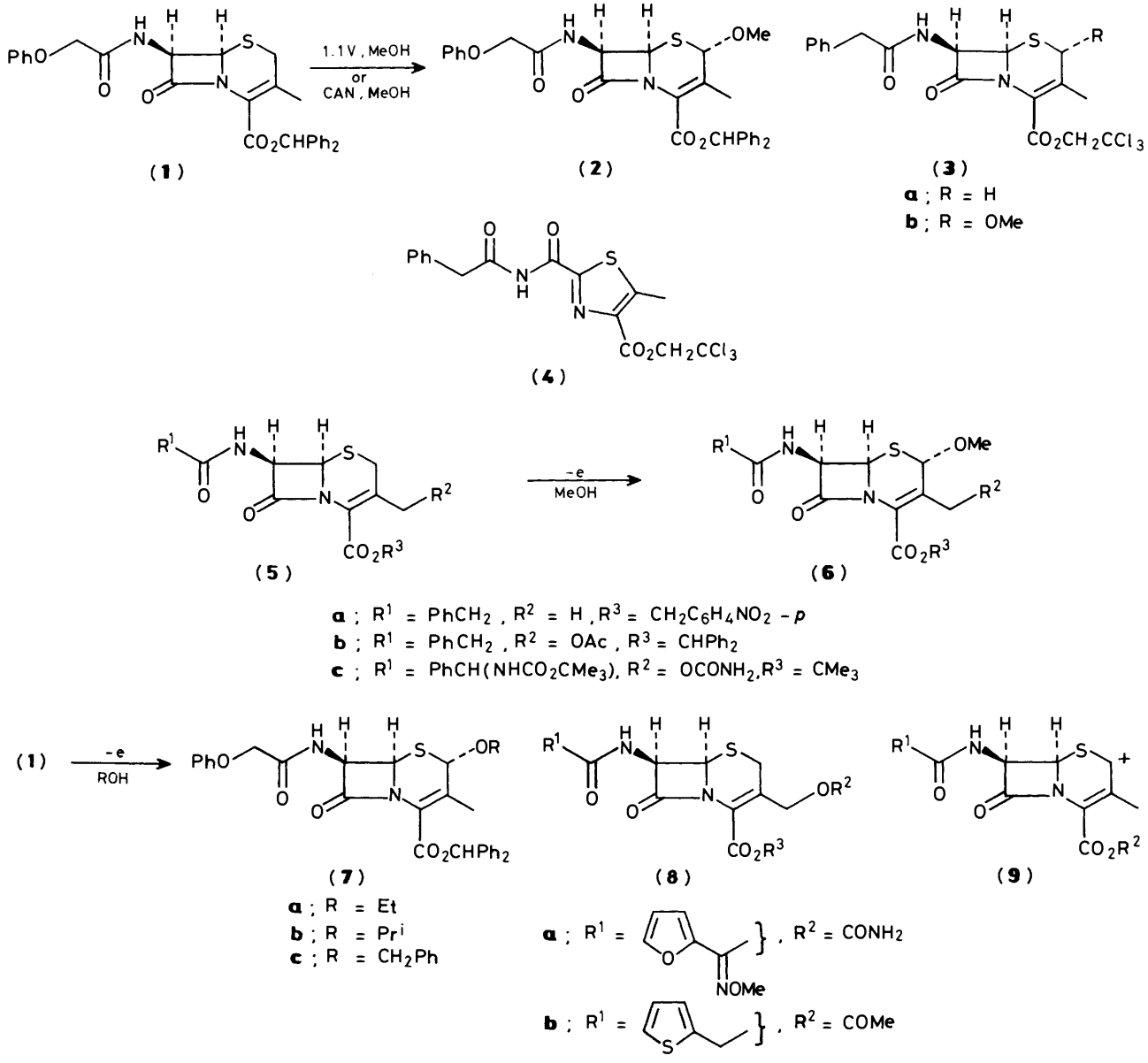
Experimental

M.p.s are corrected. Optical rotations were measured at 21 °C for 1% solutions in chloroform. U.v. spectra were recorded for solutions in ethanol; i.r. spectra were determined for solutions in bromoform. N.m.r. spectra were measured for solutions in deuteriochloroform with a Bruker AM250 FT spectrometer.

Silica gel for chromatography was Merck Kieselgel 60(7734). 'Ether' refers to diethyl ether, and light petroleum to the fraction of b.p. 60—80 °C. Solutions in organic solvents were dried over anhydrous magnesium sulphate.

Electrochemical Oxidations of Ceph-3-em Esters: General Procedure.—Electrolyses were carried out in a conventional H-cell fitted with carbon electrodes; the compartments were divided by a glass sinter. Potentials were maintained by using a Hi-Tek potentiostat (DT 2101), and measured relative to a silver–silver perchlorate reference electrode. The ceph-3-em ester (0.1 g) was added to a solution of tetraethylammonium tosylate (1.2 g) in methanol 30 ml) and tetrahydrofuran (10 ml), and the resulting solution was electrolysed at 1.1—1.2 V for 1.5—3 h. The solution was evaporated to dryness under reduced pressure, and the residue was diluted with water (10 ml) and extracted with dichloromethane (3 × 20 ml). Evaporation of the dried organic extracts left a residue (*ca.* 0.95 g). Chromatography on silica gel, followed by crystallisation gave the α-methoxylated ceph-3-em ester.

Oxidations with Cerium(IV) Ammonium Nitrate (CAN): General Procedure.—A solution of CAN (19.4 mmol) in methanol (25 ml) was added over 0.5 h to a stirred solution of the ceph-3-em ester (1 g, 1.94 mmol) in tetrahydrofuran (10 ml) and methanol (10 ml). The solution was stirred at room temperature for 3.5 h, then poured into ice–water (250 ml)



containing sodium disulphite (2.5 g), and extracted with dichloromethane (3 × 50 ml). The combined organic extracts were washed successively with aqueous 5% sodium hydrogen carbonate (50 ml) and water (50 ml), then dried and evaporated under reduced pressure to leave an orange solid (*ca.* 1 g). Chromatography on silica gel (50 g), followed by crystallisation, then gave the α-methoxylated ceph-3-em ester.

(2S,6R,7R)-*Diphenylmethyl* 2-*Methoxy*-3-*methyl*-7-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* (**2**).—Electrolysis of the ceph-3-em ester (**1**) (0.1 g)[5] at 1.1 V for 2.5 h, according to the general procedure, followed by chromatography (20:1 CH_2Cl_2–EtOAc) and crystallisation gave the 2-methoxy-4-carboxylate (0.72 g, 67%) as white prisms, m.p. 144—145 °C (from ether) (lit.,[6] 132—133 °C), $[\alpha]_D$ +116°; $\lambda_{max.}$ 265 (ε 10 850), 268 (10 850), and 274infl nm (8 900); $\nu_{max.}$ 3 410, 2 830, 1 790, 1 730, 1 694, and 1 520 cm^{-1}; δ_H 2.13 (=CMe), 3.46 (OMe), 4.58 (CH_2), 4.78 (2-H), 5.11 (d, *J* 4 Hz, 6-H), 5.96 (dd, *J* 8 and 4 Hz, 7-H), 6.96 (d, *J* 7 Hz, 2- and 6-H of PhO), 6.99 ($CHPh_2$), 7.06 (t, *J* 7, 4-H of PhO), and 7.2—7.4 (m, 13 H) (Found: C, 66.1; H, 5.2; N, 5.0; S, 6.1. Calc. for $C_{30}H_{28}N_2O_6S$: C, 66.2; H, 5.2; N, 5.1; S, 5.9%).

The same compound was prepared in 54% yield by oxidation of (**1**) with CAN.

(2S,6R,7R)-2,2,2-*Trichloroethyl* 2-*Methoxy*-3-*methyl*-7-*phenylacetamidoceph*-3-*em*-4-*carboxylate* (**3b**).—Electrolysis of (6*R*,7*R*)-2,2,2-trichloroethyl 3-methyl-7-phenylacetamidoceph-3-em-4-carboxylate (**3a**)[8] at 1.2 V for 1.5 h, according to the general procedure, followed by chromatography and crystallisation, gave the 2-methoxy-4-carboxylate (0.4 g, 40%) as white prisms, m.p. 134—135 °C, mixed m.p. 132—134 °C with authentic material (lit.,[9] m.p. 133.5—134 °C), which showed spectroscopic data identical with those of the compound synthesized by oxidation of (**3a**) with CAN.[10]

(2S,6R,7R)-4-*Nitrobenzyl* 2-*Methoxy*-3-*methyl*-7-*phenylacetamidoceph*-3-*em*-4-*carboxylate* (**6a**).—By the general procedure, treatment of the ceph-3-em ester (**5a**)[12] with CAN, followed by chromatography (9:1 dichloromethane–ether) and crystallisation, gave the 2-*methoxy*-4-*carboxylate* (47%) as colourless feathery needles, m.p. 166—168 °C (from ether), $[\alpha]_D$ +122.5°; $\lambda_{max.}$ 266 nm (ε 20 700); $\nu_{max.}$ 3 420, 2 830, 1 784, 1 734,

1 682, and 1 520 cm^{-1}; δ_H[$(CD_3)_2SO$] 2.09 (=CMe), 3.34 (OMe), 3.55 (d, *J* 15 Hz, CH*H*Ph), 3.63 (d, *J* 15 Hz, C*H*HPh), 5.03 (d, *J* 5 Hz, 6-H), 5.25 (2-H), 5.43 (d, *J* 13 Hz, CO_2CHH), 5.51 (d, *J* 13 Hz, CO_2CHH), 5.83 (dd, *J* 8 and 5 Hz, 7-H), 7.34 (m, C_6H_5), 7.74 (d, *J* 8 Hz, 2- and 6-H of C_6H_4), 8.28 (d, *J* 8 Hz, 3- and 5-H of C_6H_4), and 1.2 (d, *J* 8 Hz, NH) (Found: C, 57.8; H, 4.6; N, 8.4; S, 6.4. $C_{24}H_{23}N_3O_7S$ requires C, 57.9; H, 4.7; N, 8.45; S, 6.4%).

The same compound was produced in 24% yield when (**3**) was electrolysed at 1.1 V for 3 h.

(2S,6R,7R)-*Diphenylmethyl* 3-*Acetoxymethyl*-2-*methoxy*-7-*phenylacetamidoceph*-3-*em*-4-*carboxylate* (**6b**).—By the general procedure, treatment of the ceph-3-em ester (**5b**)[13] with CAN, followed by chromatography (3:2 light petroleum–ethyl acetate) and crystallisation gave the 2-*methoxy*-4-*carboxylate* (15%; 40% based on recovered starting material) as colourless prisms, m.p. 154—155 °C (from ether), $[\alpha]_D$ +60°; $\lambda_{max.}$ 265 nm (ε 10 200); $\nu_{max.}$ 3 410, 2 820, 1 790, 1 732, 1 680, and 1 502 cm^{-1}; δ_H 1.97 ($OCOCH_3$), 3.4 (OMe), 3.58 (d, *J* 15 Hz, C*H*HPh), 3.68 (d, *J* 15 Hz, CH*H*Ph), 4.7 (d, *J* 13 Hz, 3-C*H*H), 4.94 (d, *J* 13 Hz, 3-CH*H*), 4.98 (2-H), 5.05 (d, *J* 5 Hz, 6-H), 5.91 (dd, *J* 9 and 5 Hz, 7-H), 6.1 (d, *J* 9 Hz, NH), 6.97 ($CHPh_2$), and 2.34 (m, 15 H) (Found: C, 65.4; H, 5.1; N, 4.7; S, 5.5. $C_{32}H_{28}N_2O_7S$ requires C, 65.7; H, 4.8: N, 4.8; S, 5.5%).

(6R,7R)-*t-Butyl* 3-*Carbamoyloxymethyl*-7-[(2R)-2-*phenyl*-2-(*t-butoxycarbonylamino*)*acetamido*]*ceph*-3-*em*-4-*carboxylate* (**5c**).—A solution of trichloroacetyl isocyanate (0.212M) in dichloromethane (23 ml; 4.86 mmol) was added to a stirred solution of (6*R*,7*R*)-t-butyl 3-hydroxymethyl-7-[(2*R*)-2-phenyl-2-(t-butoxycarbonylamino)acetamido]ceph-3-em-4-carboxylate (2.3 g, 4.42 mmol)[14] in dichloromethane (25 ml), and the resulting solution was stirred at 25 °C for 2 h. More trichloroacetyl isocyanate 0.212M) in dichloromethane (2 ml; 0.44 mmol) was added, and the solution was kept in a refrigerator overnight. The solution was evaporated under reduced pressure to leave a yellow foam, which was dissolved in methanol (30 ml) and treated with a solution of sodium hydrogen carbonate (1.86 g) in water (20 ml). The cloudy suspension was stirred at 25 °C for 1.5 h, then diluted with water (250 ml) and extracted with chloroform (3 × 100 ml). The combined extracts were washed with water (100 ml), dried, and evaporated to leave a yellow gelatinous solid (2.33 g). Chromatography on silica (100 g) [2:1 ethyl acetate–light petroleum as eluant], followed by crystallisation, gave the *ester* (0.97 g, 39%) as colourless crystals, m.p. 183—184 °C (from ether), $[\alpha]_D$ +0°; $\lambda_{max.}$ 264 nm (7 480); $\nu_{max.}$ 3 430, 3 330, 3 270, 3 210, 1 780, 1 705, 1 690, 1 665, and 1 520 cm^{-1}; δ_H 1.39 (CMe_3), 1.47 (CMe_3), 3.35 (d, *J* 18 Hz, 2-C*H*H), 3.52 (d, *J* 18 Hz, 2-CH*H*), 4.53 (d, *J* 13 Hz, 3-C*H*H), 4.79 (d, *J* 13 Hz. 3-CH*H*), 5.06 (d, *J* 4 Hz, 6-H), 5.36 (d, *J* 9 Hz, C*H*NH), 5.73 (dd, *J* 9 and 4 Hz, 7-H), and 6.56 (br, $CONH_2$) (Found: C, 55.8; H, 6.3; N, 10.0; S, 5.4. $C_{26}H_{34}N_4O_8S$ requires C, 55.5; H, 6.1: N, 10.0; S, 5.7%).

(2S,6R,7R)-*t-Butyl* 3-*Carbamoyloxymethyl*-2-*methoxy*-7-[2R]-2-*phenyl*-2-(*t-butoxycarbonylamino*)*acetamido*]*ceph*-3-*em*-4-*carboxylate* (**6c**).—By the general procedure, treatment of the ceph-3-em ester (**5c**) (0.5 g) with CAN (10 equiv.), followed by chromatography (4:1 chloroform–ethanol) gave the 2-*methoxy*-4-*carboxylate* (0.11 g, 21%) as a colourless foam, $[\alpha]_D$ +20.5°; $\lambda_{max.}$ 264.5 nm (ε 6 580); $\nu_{max.}$ 3 540, 3 420, 2 825, 1 788, 1 725, 1 695, 1 580, 1 510, and 1 490 cm^{-1}; δ_H 1.43 (CMe_3), 1.52 (CMe_3), 3.4 (OMe), 4.73 (br, NH_2), 4.78 (d, *J* 12 Hz, 3-C*H*H), 5.0 (d, *J* 12 Hz). 3-CH*H*), 4.99 (2-H), 5.02 (d, *J* 5 Hz, 6-H), 5.21 (d, *J* 5 Hz, CHN*H*), 5.6 (d, *J* 5 Hz, C*H*NH), 5.86 (dd, *J* 9 and 5 Hz, 7-H), 6.63 (d. *J* 9 Hz, CONH), and 7.37 (C_6H_5) (Found: C, 54.4; H, 6.3; N, 9.15; S, 5.2. $C_{27}H_{36}N_4O_9S$ requires C, 54.7; H, 6.1; N, 9.45; S, 5.4%).

(2S,6R,7R)-*Diphenylmethyl* 2-*Ethoxy*-3-*methyl*-7-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* (**7a**).—By the general procedure, electrolysis of the ceph-3-em ester (**1**)[5] in ethanol at 1.1 V for 7.5 h, followed by chromatography (3:1 light petroleum–ethyl acetate) and crystallisation gave the 2-*ethoxy*-4-*carboxylate* (12%; 35% based on recovered starting material) as colourless fluffy needles, m.p. 151—153 °C (from ether), $[\alpha]_D$ +105°; $\lambda_{max.}$ 265 (ε 10 500), 268 (10 600), and 274infl nm (8 600); $\nu_{max.}$ 3 405, 1 785, 1 728, 1 690, and 1 520 cm^{-1}; δ_H 1.23 (t, *J* 7 Hz, CH_2CH_3), 2.12 (=CMe), 3.45 (dq, *J* 9 and 7 Hz, CH_2CH_3), 3.92 (dq, *J* 9 and 7 Hz, CH_2CH_3), 4.56 (OCH_2), 4.86 (2-H), 5.13 (d, *J* 5 Hz, 6-H), 5.96 (dd, *J* 9 and 5 Hz, 7-H), 6.94 (d, *J* 8 Hz, 2-and 6-H of PhO), 6.97 ($CHPh_2$), 7.04 (t, *J* 8 Hz, 4-H of PhO), and 7.2—7.5 (m, 13 H) (Found: C 66.4; H, 5.4; N, 5.0; S, 5.7. $C_{31}H_{30}N_2O_6S$ requires C, 66.65; H, 5.4; N, 5.0; S, 5.7%).

The same compound was produced in 59% yield when the ceph-3-em ester (**1**) was treated with CAN.

(2S,6R,7R)-*Diphenylmethyl* 2-*Isopropoxy*-3-*methyl*-7-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* (**7b**).—By the general procedure, treatment of the ceph-3-em ester (**1**)[5] with CAN in propan-2-ol, followed by chromatography (3:1 light petroleum–ethyl acetate) and crystallisation gave the 2-*isopropoxy*-4-*carboxylate* (0.47 g, 43%; 58% based on recovered starting material) as colourless fluffy needles, m.p. 99—101 °C (from ethanol), $[\alpha]_D$ +106°; $\lambda_{max.}$ 266 (ε 11 100), 268.5 (11 100), and 273.5infl nm (9 400); $\nu_{max.}$ 3 410, 1 785, 1 728, 1 690, and 1 518 cm^{-1}; δ_H 1.18 (d, *J* 6 Hz, CH*Me*), 1.21 (d, *J* 6 Hz, CH*Me*), 2.1 (3-Me), 4.01 (m, $CHMe_2$), 4.57 (OCH_2), 4.93 (2-H), 5.15 (d, *J* 5 Hz, 6-H), 5.97 (dd, *J* 9 and 5 Hz, 7-H), 6.93 (d, *J* 8 Hz, 2- and 6-H of PhO), 6.97 ($CHPh_2$), 7.04 (t, *J* 8 Hz, 4-H of PhO), and 7.2—7.5 (m, 13 H) (Found: C, 66.9; H, 5.6; N, 4.8; S, 5.6. $C_{32}H_{31}N_2O_6S$ requires C, 67.1; H, 5.6; N, 4.9; S, 5.6%).

The same compound was produced in 15% yield (not optimised) when the ceph-3-em ester (**1**) was electrolysed at 1.1 V under the usual conditions.

(2S,6R,7R)-*Diphenylmethyl* 2-*Benzyloxy*-3-*methyl*-7-*phenoxyacetamidoceph*-3-*em*-4-*carboxylate* (**7c**).—By the general procedure, treatment of the ceph-3-em ester (**1**)[5] with CAN in benzyl alcohol, followed by chromatography (2:1 ethyl acetate–light petroleum) and crystallisation, gave the 2-*benzyloxy*-4-*carboxylate* (32%) as colourless prisms, m.p. 143—145 °C (from ether), $[\alpha]_D$ +124°; $\lambda_{max.}$ 265 (ε 12 350), 268.5 (12 410), and 273.5infl nm (9 200); $\nu_{max.}$ 3 400, 1 785, 1 728, 1 690, and 1 518 cm^{-1}; δ_H 2.01 (3-Me), 4.53 (d, *J* 11 Hz, C*H*HPh), 4.58 (OCH_2), 4.85 (d, *J* 11 Hz, CH*H*Ph), 4.9 (2-H), 5.19 (d, *J* 5 Hz, 6-H), 5.97 (dd, *J* 9 and 5 Hz, 7-H), 6.94 (d, *J* 8 Hz, 2- and 6-H of PhO), 6.97 ($CHPh_2$), 7.06 (t, *J* 8 Hz, 4-H of PhO), and 7.2—7.5 (m, 18 H) (Found: C, 69.7; H, 5.2; N, 4.2; S, 5.2. $C_{36}H_{32}N_2O_6S$ requires C 69.7; H, 5.2; N, 4.5; S, 4.9%).

The same compound was produced in 21% yield (not optimised) when the ceph-3-em ester (**1**) was electrolysed at 1.1 V under the usual conditions.

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