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NEW METHODOLOGY FOR C-4 SUBSTITUTION AND SULPHOXIDE DE-OXYGENATION REACTIONS IN CEPH-3-EMS.

David H. Bremner*, Neil S. Ringan and (in part) Alistair D.M. Smith

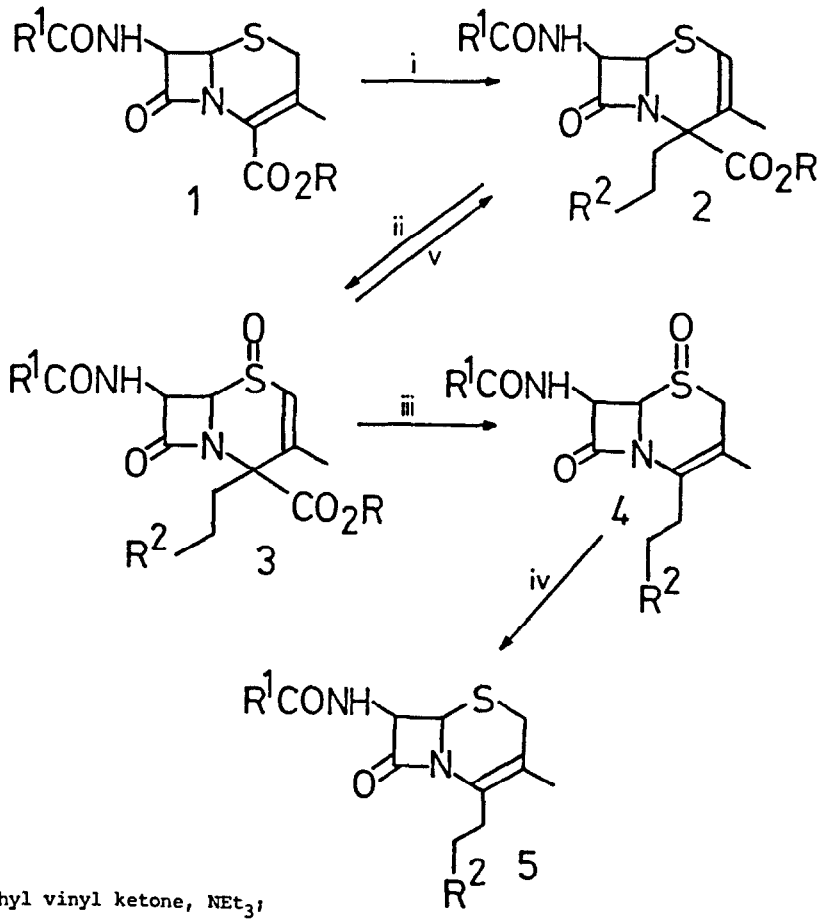
Dundee College of Technology, Bell Street, Dundee DD1 1HG

SUMMARY: Addition of Michael acceptors to the C-4 position in ceph-3-ems followed by oxidation, de-esterification, and de-carboxylation results in the formation of new 4-monosubstituted ceph-3-ems; an unusually mild de-oxygenation process for ceph-2-em sulphoxides is also described.

The introduction of new functional groups at the C-4 position of ceph-3-ems has been achieved, almost exclusively, by manipulation of the C-4 carboxylic acid group. Thus the C-4 acid functionality has been converted into the acid chloride and thence to a number of polar groupings *via* the diazoketone[1a,b]. Furthermore, cephalosporin-4-aldehyde derivatives formed by Moffatt oxidation of the corresponding 4-hydroxymethylcephalosporins have been transformed into acrylic acid derivatives which are 4-vinylogues of the parent cephalosporins[2]. However, as C-4 disubstituted ceph-3-ems are easily prepared[3], we believed that de-esterification, followed by de-carboxylation would lead to novel C-4 monosubstituted products. We now describe new synthetic methodology which provides ceph-2-ems with substituted ethyl groups attached directly to C-4 in place of the original carboxyl group. In addition we report a surprisingly facile procedure for the de-oxygenation of ceph-2-em sulphoxides.

When (6R,7R)-diphenylmethyl-3-methyl-7-phenoxyacetamidoceph-3-em-4-carboxylate (1,R=$CHPh_2$) was treated with a catalytic amount of triethylamine in methyl vinyl ketone as reactant and solvent, it was smoothly transformed into a slightly more polar product After rapid short-path chromatography the Michael adduct (2,R=$CHPh_2$), which crystallised from petrol/ethyl acetate, was obtained in 90% yield[4]. Removal of the diphenylmethyl ester function with anisole-trifluoroacetic acid[5] afforded an 80% yield of the expected carboxylic acid (2,R=H)[6] which did not de-carboxylate when treated with base at room temperature.

Oxidation of sulphide (2,R=$CHPh_2$) with m-chloroperoxybenzoic acid gave the sulphoxide (3,R=$CHPh_2$;85% yield) which was smoothly de-esterified (anisole-trifluoroacetic acid) to produce the corresponding carboxylic acid as an unstable crystalline solid (3,R=H;77%). When (3,R=H) was stirred in acetone containing a catalytic amount of triethylamine a flocculent white precipitate appeared almost immediately. After continued stirring overnight, the de-carboxylated ceph-3-em (4;87% yield) was isolated[8]. The driving force for this reaction is the greater thermodynamic stability of β,γ -unsaturated sulphoxides over the corresponding α,β -unsaturated sulphoxides[9], with the possible involvement of the sulphoxide oxygen in the de-carboxylation sequence.



Reagents:

(i) Methyl vinyl ketone, NEt_3;
(ii) m-CPBA, MDC;
(iii) Anisole-TFA;
(iv) P_2S_5/Pyr;
(v) Zn-HOAc.

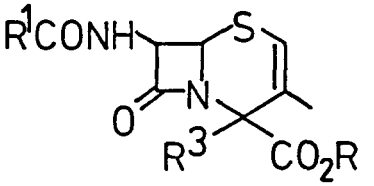
$R^1 = PhOCH_2-$

$R^2 = -COCH_3$

De-oxygenation of ketone (4) with PBr_3/DMF gave a complex reaction mixture but P_2S_5/pyridine in dichloromethane[10] completed the sequence to afford the sulphide (5;70%)[11]. Other Michael acceptors which have been added at C-4 and hence converted into new C-4 monosubstituted products include acrylonitrile, dimethyl butynedioate, and methyl acrylate.

While investigating the chemistry of C-4 disubstituted compounds, we discovered an unusually mild de-oxygenation procedure for ceph-2-em sulphoxides. When a solution of (3,R=$CHPh_2$) was stirred for several hours with zinc in DMF containing glacial acetic acid[12] it was converted to the sulphide (2,R=$CHPh_2$;89%). No ceph-3-em sulphoxides were found to de-oxygenate under similar conditions. Normal de-oxygenation of ceph-3-em sulphoxides requires activating agents such as acetyl chloride used in conjunction with

reducing agents. This has been attributed to the enhanced stability of ceph-3-em sulphoxides due to electronic factors[13]. Obviously, no such electronic effects exist in ceph-2-em sulphoxides, as the sulphides (6,R=$CHPh_2$;R^3=CH_2CH_2CN;95%,foam), and (7,R=$CHPh_2$; R^3=$CH_2CH_2CO_2CH_3$;80%;oil) were easily prepared by zinc-acetic acid treatment of the corresponding sulphoxides. When the oxidised adduct from cephem (1,R=$CHPh_2$) and dimethyl butynedioate was treated under these reducing conditions, simultaneous sulphoxide de-oxygenation and di-ester double bond reduction occurred to produce (8,R=$CHPh_2$; R^3=$CH(CO_2CH_3)CH_2CO_2CH_3$;75%)[14].



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4. Compound 2(R=$CHPh_2$); m.p. 108-109°C; νmax(KBr) 1770, 1742, 1710 and 1690 cm^{-1}; δ($CDCl_3$) 1.75(3H,d,J=1.0 Hz), 2.09(3H,s), 2.32-2.93(4H,m), 4.56(2H,s), 5.22 (1H,d,J=4.5 Hz), 5.49(1H,dd,J=4.5 and 8.8 Hz), 6.11(1H,d,J=1.0 Hz), and 6.88-7.55(17H,m). (Found C,67.81; H,5.48; N,4.79; S,5.48%. $C_{33}H_{32}N_2O_6S$ requires C,67.42; H,5.47; N,4.79; S,5.58%).
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6. Compound 2(R=H); m.p. 170-171°C; νmax(KBr) 3700-3000, 1760, 1720 and 1680 cm^{-1}; δ(d_6-DMSO) 1.70(3H,d,J=1.2 Hz), 2.10(3H,S), 2.18-2.35(2H,m), 2.52-2.72(2H,m), 4.51(2H,ABq,J=15.0 Hz), 5.10(1H,d,J=4.3 Hz), 5.29(1H,dd,J=4.3 and 7.6 Hz), 6.38(1H,d,J=1.2 Hz), 6.92-7.00(3H,m), 7.27-7.35(2H,m), and 9.12(1H,d,J=7.6 Hz). (Found C,57.30; H,5.26; N.6.52; S,7.60%. $C_{20}H_{22}N_2O_6S$ requires C,57.42; H,5.26; N,6.70; S,7.66%).

7. Compound 3(R=$CHPh_2$); m.p.175-177°C; νmax(KBr) 1770, 1730, 1700 and 1680 cm^{-1}; δ($CDCl_3$) 1.85(3H,d,J=1.0 Hz), 2.14(3H,S), 2.49-3.10(4H,m), 4.52(3H,m), 5.84(1H,dd,J=4.8 and 10.6 Hz), 6.71(1H,d,J=1.0 Hz), 6.91-7.04(4H,m), 7.22-7.42 (12H,m) and 8.21(1H,d,J=10.6 Hz). (Found C,66.13; H,5.29; N,4.61; S,5.15%. $C_{33}H_{32}N_2O_7S$ requires C,66.00; H,5.33; N,4.66; S,5.33%).

8. Compound 4; m.p. >300°C; νmax(KBr) 1761, 1703 and 1689cm^{-1}; δ($CDCl_3$) 1.85(3H,s), 2.18(3H,s), 2.68-3.03(4H,m), 3.29(2H,ABq,J=18.0 Hz), 4.41(1H,dd,J=4.6 and 1.2 Hz), 4.58(2H,s), 6.01(1H,dd,J=4.6 and 10.4 Hz), 6.92-7.06(3H,m), 7.62-7.35(2H,m), and 7.96(1H,d,J=10.4 Hz). (Found C,58.99; H,5.59; N,7.08; S,8.17%. $C_{19}H_{22}N_2O_5S$ requires C,58.46; H,5.64; N,7.18; S,8.21%).

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11. Compound 5; m.p. 160-162°C; νmax(KBr) 1760, 1700 and 1670 cm^{-1}; δ($CDCl_3$) 1.80(3H,s), 2.17(3H,s), 2.64-2.87(4H,m), 3.22(2H,ABq,J=17.3 Hz), 4.57(2H,s), 4.94(1H,d,J=4.8 Hz), 5.77(1H,dd,J=10.5 and 4.8 Hz), 6.92-7.06(3H,m) and 7.24-7.36(3H,m). (Found C,60.61; H,6.22; N,7.51; S,8.41%. $C_{19}H_{22}N_2O_4S$ requires C,60.94; H,5.92; N,7.48; S,8.56%).

12. Conditions normally used to de-protect trichloroethyl esters. R.B. Woodward, K.J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathen and H. Vorbruggen. J. Am. Chem. Soc., 1966, 88, 852.

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14. Compound 8(R=$CHPh_2$;R^3=$CH(CO_2CH_3)CH_2CO_2CH_3$); m.p. 86-90°C; νmax(KBr) 1773, 1740 and 1692 cm^{-1}; δ($CDCl_3$) 1.78(3H,d,J=1.0 Hz), 2.25(1H,dd,J=17 and 1.6 Hz), 3.02(1H,dd,J=17 and 9.4 Hz), 3.45(3H,s), 3.75(3H,s), 4.38(1H,dd,J=9.4 and 1.6 Hz), 4.54(2H,s), 5.51(1H,d,J=4.6 Hz), 5.57(1H,dd,J=9.1 and 4.6 Hz), 6.20(1H,d,J=1.0 Hz), 6.90-7.10 (4H,m) and 7.20-7.42(13H,m). (Found C,63,34; H,5.14; N,4.17; S,4.49%. $C_{35}H_{34}N_2O_9S$ requires C,63.81; H,5.20; N,4.25; S,4.89%).

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