Exceptional Oxidative Allylic Rearrangements of 4-Alkoxycarbonyl-3-methylceph-3-em 1,1-Dioxides induced by Palladium–Charcoal

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Representatives of the title compounds are converted into 4-alkoxycarbonyl-4-hydroxy-3-methylceph-2-em 1,1-dioxides by the action of palladium–charcoal in ethyl acetate; an X-ray analysis of one of the products reveals that the 4-hydroxy function is α -oriented.

Recently, two of us described¹ a synthesis of the cephem dioxide (1a) and its conversion into the acid (1b) under hydrogenolytic conditions (H₂, 10% Pd–C, EtOAc). We now report on a remarkable oxidative rearrangement which was encountered when compound (1a) was left in ethyl acetate containing 5% palladium–charcoal.

On one occasion [in which a solution of the cephem dioxide (1a) in EtOAc had been left in contact with 5% Pd-C for a few hours prior to treatment with H_2], a mixture of acids was produced. Crystallisation of the mixture from acetone-light petroleum provided the known acid (1b) in 23% yield. Treatment of the mother liquor in acetone with an ethereal solution of sodium 2-ethylhexanoate gave an unknown sodium salt [the weight of which matched that of the acid (1b)], m.p. 157-160 °C, $[\alpha]_D$ -126° (EtOH-H₂O). On the basis of its spectroscopic properties, the sodium salt was considered to possess the partial structure (2). Thus the i.r. spectrum featured strong absorptions at 1770 and 1640 cm⁻¹ (for the β -lactam and carboxylate moieties) and the 300 MHz ¹H n.m.r. spectrum (D_2O) showed a three-proton doublet (J 1.3 Hz) at δ 1.74 (for the 3-methyl group) which was coupled to a one-proton multiplet at δ 6.42 (for the 2-proton).

A clue as to the identity and origin of the unknown sodium salt came when a solution of the benzyl ester (1a) in ethyl acetate was stirred with 5% palladium-charcoal (4 mass equiv.) for 3 h in the absence of hydrogen. The more polar syrupy product (57% yield after SiO₂ chromatography), $[\alpha]_D$ -33° (EtOH), which emerged, was identified as the hydroxyderivative (3a). As well as showing a molecular ion at m/z337.0732 (corresponding to C₁₅H₁₅NO₆S) in its mass spectrum, the material possessed an absorption at 3 410 cm⁻¹ in its i.r. spectrum and a broad signal at δ 4.8 (which disappeared on adding D₂O) in its ¹H n.m.r. spectrum (CDCl₃). Furthermore, the compound reacted with acetic anhydride-pyridine to give the O-acetyl derivative (**3b**) (59% yield after SiO₂ chromatography), $[\alpha]_D - 15^\circ$ (EtOH). Evidently, the salt possessed the structure (**2**), X = OH, and it arose by hydrogenolysis of the hydroxy-derivative (**3a**).

The cephem dioxide (4a), m.p. 184–187 °C, $[\alpha]_D -55^{\circ}$ (CDCl₃-EtOH), prepared in 93% yield by oxidation of the cephem (4b) with 30% hydrogen peroxide-formic acid in dichloromethane,² reacted in an analogous manner with 5% palladium-charcoal (4 mass equiv.) in ethyl acetate. Following silica-gel purification, the hydroxy-derivative (5a), m.p. 79–81 °C, $[\alpha]_D -28^{\circ}$ (EtOH), was obtained in 60% yield. It was converted into the acetate (5b), m.p. 74–77 °C, $[\alpha]_D -17^{\circ}$ (EtOH), by the action of acetic anhydride-pyridine.

That the hydroxy-function of compound (5a) was α -oriented was established by a single-crystal X-ray analysis: the molecular structure is shown in Figure 1. Crystal data: $C_{29}H_{26}N_2O_8S.C_4H_{10}O, M = 636.7$, orthorhombic, space group $P2_12_12_1$, a = 10.356(2), b = 11.107(3), c = 29.020(7) Å, U = 3338 Å³, Z = 4, $D_c = 1.27$ g cm⁻³. 2115 Independent observed reflections $[|F_o|] > 3\sigma(|F_o|)$, $\theta \le 58^\circ$] were measured on a Nicolet R3m diffractometer with $Cu-K_{\alpha}$ radiation (graphite monochromator) using ω -scans. The structure was solved by direct methods and refined anisotropically to R =0.052, $R_w = 0.059$. The asymmetric unit contains one molecule of diethyl ether which is severely disordered. The hydroxy oxygen, O(4), is involved in an intramolecular hydrogen bond (2.78 Å, $O \cdot \cdot \cdot H = 1.96$ Å, $O-H \cdot \cdot \cdot O$ angle = 142°) to the oxygen of the ether molecule. N(25) is within hydrogen-bonding distance of both O(28), 2.52 Å, and O(2), 2.83 Å; the H(25) $\cdot \cdot \cdot O(28)$ and H(25) $\cdot \cdot \cdot O(2)$ distances are 1.87 and 2.27 Å respectively.‡

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[‡] The atomic co-ordinates are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K. Any request should be accompanied by the full literature citation for this communication.



Trifluoracetic acid reacted with the diphenylmethyl ester (**5a**) to give the acid (**5c**) (77% yield), m.p. 137–139 °C, which was transformed into the sodium salt (**5d**) (62% yield), m.p. 136–139 °C, $[\alpha]_D$ – 19°. In common with its relative (**2a**) (which is presumed to possess a similar geometry at position 4), the sodium salt (**5d**) showed no antibacterial activity and failed to synergise the action of ampicillin against β -lactamase-producing bacteria [compounds (**2a**) and (**5d**) were stable in aqueous solution].

d; $R^1 = N\alpha$, $R^2 = H$

The $(1a) \rightarrow (3a)$ and $(4a) \rightarrow (5a)$ transformations are remarkable reactions. The sulphones and ester moieties appear to be important structural features for the oxidative rearrangements. Thus the cephem (4b) and the cephem 1-oxide (4c) [prepared in 51% yield by oxidation of the



Figure 1. The molecular structure of compound (5a).

cephem (4b) with 30% H_2O_2 -HOAc- $CH_2Cl_2^2$], m.p. 191– 193 °C, $[\alpha]_D$ +24° (EtOH), failed to react with palladiumcharcoal in ethyl acetate. Similarly, the acid (4d) [obtained by treating the ester (4a) with CF₃CO₂H and containing *ca.* 20% of an impurity], m.p. 144–146 °C, was unaffected by the reagent.

It is noteworthy that the oxidations, which were not impeded when conducted in an atmosphere of argon, required ca. 1 atom equiv. of palladium per mol equiv. of cephem dioxide and were not noticeably influenced by the addition of small amounts of water or methanol.

The present results are of interest in three respects. First, to our knowledge the palladium-induced oxidative allylic rearrangements are novel reactions; clearly, the scope and mechanism of these processes are deserving of further study. Secondly, oxidative allylic rearrangements of ceph-3-em derivatives are relatively rare; hitherto, only methylthiolations (base-MeSO₂SMe)³ and ethoxycarbonylaminations [NaN(Cl)CO₂Et]⁴ have been described. Finally, the species (**3a**) and (**5a**) are potentially useful precursors of novel β -lactam derivatives.

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