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OZONOLYSIS OF ETHYLIDENE AZETIDINONES; OZONIDE FRAGMENTATION TO α-AMINO ACID-N-CARBOXYANHYDRIDES

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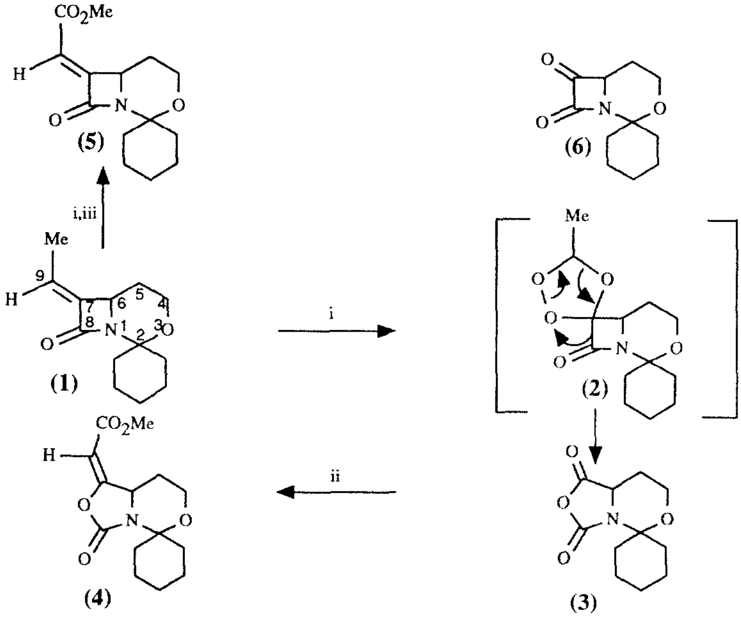
SUMMARY:

Ozonolysis of α-ethylidene azetidinones (1) and (10) did not provide the expected α-oxoazetidinones, but afforded α-amino acid-N-carboxyanhydrides (3) and (11).

Azetidin-2,3-diones (α-keto-ß-lactams) (*cf.* 7) have been prepared in many areas of ß-lactam chemistry, and have found utility as reactive synthetic intermediates. Although monocyclic examples[1,2] have been reported, the greatest number of investigations has involved 6-oxopenicillins.[3-10] Some groups have also studied 7-oxocephalosporins.[8,9,11] Other reports have described their use as substrates for amination reactions leading to the nocardicins,[12] and for tranformations to a variety of substituted vinylidene ß-lactam derivatives.[5,10,13,14] Baldwin has discovered an interesting ring expansion reaction of benzyl 6-oxopenicillanate; treatment with an excess of diazomethane gave an oxo-γ-lactam.[15]

In the course of our investigations into the synthesis of functionalised carbapenems we ozonolysed the protected *E*-ethylidene azetidinone (1).[16,17] On subjecting the resulting ozonide solution to the usual work-up conditions using either triphenylphosphine or dimethyl sulphide, we did not obtain an α-keto derivative (6). To our surprise, the colourless product m.p. 130-132°C contained an extra oxygen atom ($C_{11}H_{15}NO_4$, CHN, precise mass MS measurement). Although the 1R spectrum [υ_{max} ($CHCl_3$) 1 850 and 1 780cm^{-1}] exhibited similar frequency bands to those reported for benzyl 6-oxopenicillanate [υ_{max} ($CHCl_3$) 1 830 and 1 780cm^{-1}], it displayed a distinctive 'anhydride-like' carbonyl group profile. There was no strong UV absorption [*cf.* (7), λ_{max} 350nm].[1] The combined evidence supported a cyclic α-amino acid-N-carboxyanhydride structure (3).[19] Later experiments showed that neither Ph_3P nor Me_2S is necessary for the reaction to occur. This may be rationalised in terms of an acyl migration mechanism for ozonide (2), which leads, with loss of acetaldehyde (arrows), to anhydride (3) (83%). It is related to the mechanism proposed[20] by Bailey for the so-called 'anomalous' ozonolysis reaction of acylic enones and enoates. Acyl migration to peroxide oxygen is proposed by analogy with the Baeyer-Villiger Rearrangement.



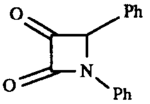
Reagents: i, O_3, EtOAc, -70°, 3 min. ii, Ph_3P: $CHCO_2Me$, EtOAc, Δ, 30 min. iii, Ph_3P: $CHCO_2Me$, -70-0°C, 1h.

When anhydride (**3**) in ethyl acetate was treated with carbomethoxymethylene triphenylphosphorane, no reaction was observed at room temperature. This is further evidence for the absence of the reactive α-keto-ß-lactam carbonyl functionality. At reflux temperature a single acrylate derivative (**4**) ($C_{14}H_{19}NO_5$) was obtained (81%, m.p. 103-104°C) [λ_{max} (EtOH) 238nm; ν_{max} ($CHCl_3$) 1 800, 1 710, and 1 665cm^{-1}].[19] In contrast, when the stabilised phosphorane (1.1 mol equiv.) was added to the cold (-70°C) solution of ozonide (**2**) and the reaction mixture allowed to warm to room temperature, a different acrylate (**5**) was produced (57%) ($C_{14}H_{19}NO_4$) m.p. 108-110°C [λ_{max} (EtOH) 266 and 218nm; υ_{max} ($CHCl_3$) 1 750, 1 730, and 1 710cm^{-1}].[19] The compound so obtained is the derivative of the α-ketolactam (**6**). However, owing to the propensity of precursor ozonide (**2**) to rearrange/fragment to anhydride (**3**) (*vide supra*) we believe that acrylate (**5**) arises directly by attack of phosphorane at C-7 of ozonide (**2**).[21] At no time in our reaction sequences did we obtain a compound exhibiting the expected properties of ketolactam (**6**).

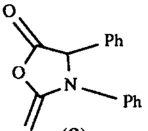
Monocyclic amino acid-N-carboxyanhydrides (eg. **8**) have been obtained by Palomo[2] by *m*-chloroperbenzoic acid oxidation of azetidin-2,3-diones (eg. **7**).

We have also observed the ozonide fragmentation in a different carbapenem series. Ozonolysis of the homochiral *E*-ethylidene compound (**10**), obtained from the tricylic cyclopropane system (**9**)[22] by a mesylation/DBU elimination sequence, gave anhydride (**11**) [υ_{max} ($CHCl_3$) 1 850, 1 795cm^{-1}]. This highly strained molecule failed to react further with the stabilised phosphorane to give an analogue corresponding to (**4**). It decomposed liberating carbon dioxide [υ_{max} ($CHCl_3$) 2335cm^{-1}]. As before, direct trapping of the ozonide with the stabilised phosphorane provided acrylate derivative (**12**) of the azetidinone. This was obtained consistently, albeit in low yield (5%). Olefins (**4**), (**5**) and (**12**) are provisionally assigned as the *E*-isomers on steric grounds.[14]

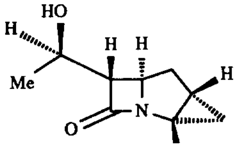
The outcome of our ozonolysis reactions using compounds (**1**) and (**10**) is at variance with results reported[23] by Tufariello for a monocyclic ethylidene ß-lactam. We therefore recommend caution in extending such reactions to polycyclic systems. Anhydrides of type (**8**) are readily opened by reactions with nucleophiles[2] and are known precursors of α-amino acid derivatives.[24]



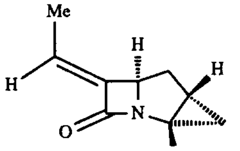
(7)



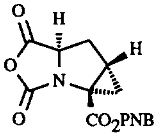
(8)



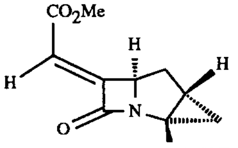
(9)



(10)



(11)



(12)

PNB = $-CH_2C_6H_4-NO_2-p$

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18. All new compounds were fully characterised by microanalysis and/or high resolution mass spectral measurements.
19. **Selected ^{1}HNMR Spectral Data:** Anhydride (**3**) δ_H ($CDCl_3$) 1.2-2.65 (12H, m), 3.93 (2H, dd, *J*8 and 4Hz, 4-H_2, one $^3J_{4,5}$=O), and 4.41 (1H, dd, *J*12 and 5Hz, 6-H). Acrylate (**4**) δ_H ($CDCl_3$) *inter alia* 3.67 (3H, s), 3.97 (2H, dm, *J*13Hz, 4-H_2), 5.19 (1H, ddd, *J*12, 4, and 2Hz, 6-H), and 5.57 (1H, d, *J*2Hz, C*H*CO_2Me). Acrylate (**5**) δ_H ($CDCl_3$) *inter alia* 3.73 (3H, s), 3.84 (2H, ddd, *J*12, 5 and 3Hz, 4-H_2), 4.39 (1H, ddd, *J*12, 6, and 1Hz, 6-H), and 6.19 (1H, d, *J ca* 1Hz, C*H*CO_2Me).
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