Tetrahedron Letters Vol. 21, pp 2451 - 2452
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0040-4039/80/0615-2451$02.00/0

COPPER (II) CATALYSED DECOMPOSITION OF PENICILLIN - DERIVED DIAZOKETONES; FORMATION OF A NOVEL FUSED β-LACTAM

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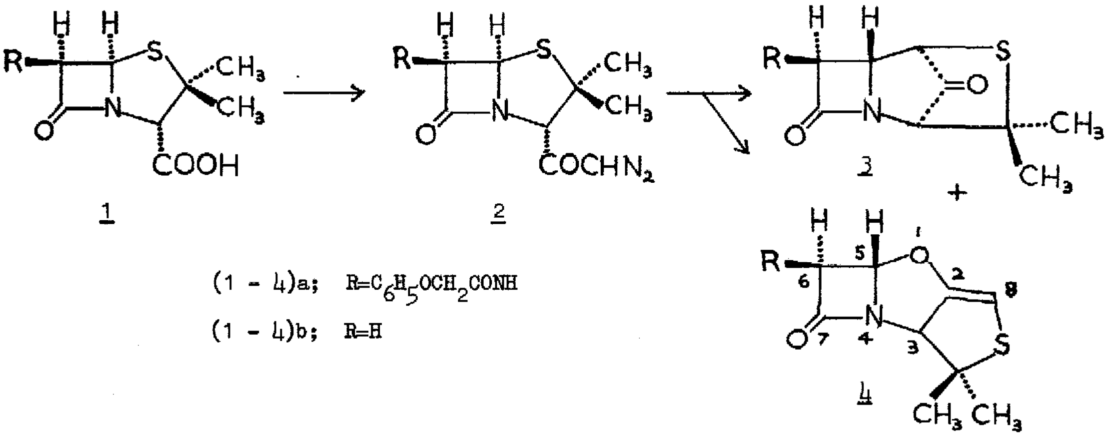
Summary: Penicillanic acid diazoketone undergoes decomposition in the presence of copper (II) acetylacetonate in benzene solution leading to the C-6 unsubstituted tricyclic ketone (3b) and the novel tricyclic oxapenam (4b) as the minor product.

The interest in the synthesis of novel fused β-lactams has been stimulated recently by the discovery of several new naturally occurring compounds such as clavulanic acid[1], thienamycin[2] and the olivanic acids[3]. The copper (II) catalysed decomposition of diazoketones of type 2a derived from 1a has been found[4] to lead to the unusual bridged tricyclic ketones of type 3a. Since these new compounds possess a carbon skeleton similar to that found in both thienamycin and the olivanic acids the reaction has been extended to include the C-6 unsubstituted compounds designed as analogues or hybrids of the new natural products.



1

2

3

4

(1 - 4)a; $R=C_6H_5OCH_2CONH$

(1 - 4)b; R=H

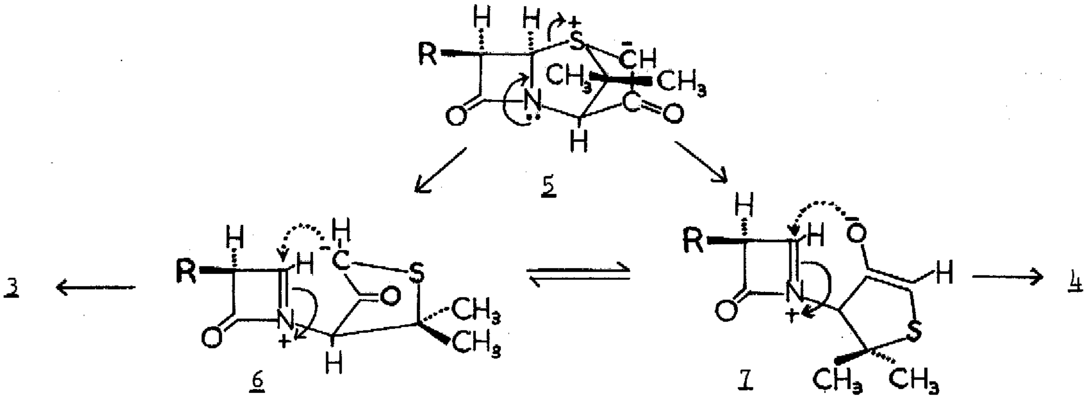
Penicillanic acid diazoketone 2b was prepared in a similar way to that described for penicillin-derived diazoketones[5] (EtOCOCl, Et_3N, CH_2Cl_2, -20°; CH_2N_2, 0°) to afford an oily product after chromatography, ν_{max} ($CHCl_3$) 2100 (diazo function) 1780 (β-lactam C=O), 1635 cm^{-1} (C=O). Treatment of the diazoketone 2b with one equivalent of copper acetylacetonate in benzene (.03 molar solution, reflux 20 mins.) gave two products which were separable by chromatography on silica gel. The expected tricyclic ketone 3b was isolated as an oil (25%) which corresponded spectroscopically with the analogous compounds described by Ernest[4], ν_{max} ($CHCl_3$) 1780 cm^{-1} (β-lactam C=O and ketonic C=O). δ ($CDCl_3$), inter alia, 3.33 and 3.57 (1H each, 2s, bridge-head

H's) and 3.92 (1H, dd, J 3 and 5 Hz, C5-H).

In addition to the tricyclic ketone a second product was isolated after chromatography as an oil (7%) which we have assigned structure 4b. In support of this structure the i.r. spectrum ($CHCl_3$) shows a β-lactam carbonyl at 1795 cm^{-1} and an absorption at 1660 cm^{-1} for a cyclic double bond adjacent to sulphur. The n.m.r. ($CDCl_3$) contained an ABX system [δ 3.07 (1H, dd, J 17 and 1 Hz, 6β-H), 3.37 (1H, dd, J 17 and 3 Hz, 6α-H) and 5.58 (1H, dd, J 3 and 1 Hz, C5-H)] which compared favourably with clavulanic acid[1]. The C-3 proton at δ 4.78 (d, J 2.5 Hz) was allylically coupled to the C-8 proton at δ 5.44 (d, J 2.5 Hz) with the gem dimethyl group appearing as a singlet at δ 1.48.

The presence of a further product from the copper (II) catalysed decomposition of penicillin V diazoketone 2a was also confirmed. The major product (3a) (as determined by n.m.r. on the crude reaction product) decomposed on chromatography but the minor product was sufficiently stable to be isolated in low yield (6%). This minor product was consistent with the assigned structure 4a ν_{max} ($CHCl_3$) 3500 (NH), 1800 (β-lactam C=O), 1700 (amide C=O), 1660 cm^{-1} (double bond). δ ($CDCl_3$), *inter alia*, 4.80 (1H, d, J 7 Hz, C6-H), 5.67 (1H, s, C5-H)[6], 4.76 (1H, d, J 2.5 Hz, C3-H) and 5.46 (1H, d, J 2.5 Hz, C8-H).

The formation of the secondary products in these reactions may be rationalised by invoking an additional species 7 to the intermediates proposed by Ernest[4]. Compound 3 may conceivably arise from 6 and formation of 4 *via* 7.



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6. No coupling with the C6-H, the dihedral angle approximating 90°.

(Received in UK 9 April 1980)