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BORON TRIFLUORIDE CATALYSED REACTIONS OF 2,2,2-TRICHLOROETHYL 6-DIAZOPENICILLANATE WITH AROMATIC ALDEHYDES: REARRANGEMENTS VIA PENAM C(5)-C(6) BOND CLEAVAGE.

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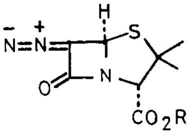
Abstract. The $BF_3.Et_2O$ catalysed reactions of diazopenicillanate **1** with aromatic aldehydes provide 2,3-dihydrothiazolo[2,3-b][1,3]oxazin-5-ones **4** via C(5)-C(6) cleavage of 6-formylpenicillanates **8**.

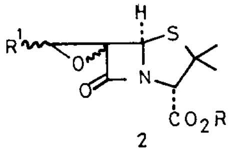
The $BF_3.Et_2O$ catalysed reactions of 6-diazopenicillanates e.g. **1**, with aliphatic aldehydes are known to provide the corresponding 6,6-spiroepoxy- and 6-acyl-penicillanates **2** and **3**.[1] Our interest in these products, as well as in the reactions of carbonyl compounds in general with **1**, prompted us to investigate the corresponding reactions of **1** with aromatic aldehydes. Subsequent to the commencement of this work, a report by Sheehan[2] appeared which conflicted with our findings and stimulated a more thorough investigation. Our results now presented clarify some ambiguities concerning the structures of the major non-β-lactam products of these reactions, and complement our recent report[3] on penicillanate rearrangements via the rarely observed cleavage of the C(5)-C(6) bond.[4]

In our hands the reaction of benzaldehyde with **1** in CH_2Cl_2 at 0°, in the presence of a catalytic amount of $BF_3.Et_2O$, gave the epoxide **2a** as the minor product (ca 1%). The major product isolated in up to 24% yield after SiO_2 chromatography was identified as the 2,3-dihydrothiazolo[2,3-b][1,3]oxazin-5-one **4a**.[5] This product appears to be identical with that reported by Sheehan[2], but to which the structure **5a** was assigned without adequate explanation of the two low field protons in the nmr spectrum, and the failure of D_2O exchange with the benzylic proton expected for **5a**. The latter structure was further excluded through ^{13}C nmr by the presence of only two carbonyl singlets, and the absence of a third lower field ketonic carbonyl resonance.

Similar reaction of p-nitrobenzaldehyde with **1** provided the epoxide **2b** (17.5%) and the thiazolooxazinone **4b** (12.6%)[5] as the major products, while reaction of anisaldehyde with **1** under the same conditions yielded a crystalline product (without recourse to chromatography) which was identified as the 6-formylpenicillanate **8b**.[6] Only one isomer of **8b** was obtained, of unassigned stereochemistry at C(6), with none of the epoxide **2c** being detected. Treatment of **8b** with either SiO_2 or $BF_3.Et_2O$ in CH_2Cl_2 at room temperature brought about immediate



1



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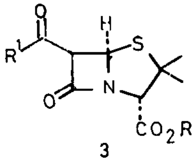

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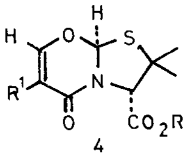

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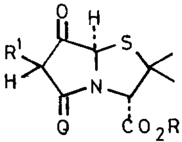

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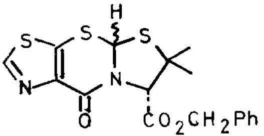
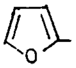


6

R = CH_2CCl_3

2 - 5 a R^1 = Ph
b R^1 = $p\text{-}O_2NC_6H_4$
c R^1 = $p\text{-}MeOC_6H_4$
d R^1 = 

rearrangement to the thiazolooxazinone 4c.[5] When however the crude product from the anisaldehyde reaction was subjected to SiO_2 chromatography, 4c was isolated directly as a crystalline solid (34%). Reaction of 1 with furfural, like that with anisaldehyde, gave the thiazolooxazinone 4d[5] with none of the epoxide 2d detected. Subsequent re-examination of the benzaldehyde reaction products using florosil chromatography also afforded a small sample of the 6-formyl derivative 8a.[6]

Unambiguous structural identification of 4c was obtained by single crystal X-ray analysis (Figure)[7] which revealed the 3S,8aS configuration. The very similar chemical shifts of the 8a protons in the nmr spectra of 4a-4d suggested the same 3S,8aS configuration for all these compounds. Unlike the analogous thiazolothiazinones 6[3], the oxazinones 4 were stable to attempted thermal epimerisation (toluene reflux) at C(8a).

Formation of the thiazolooxazinones 4 (Scheme) probably occurs by cyclisation of the thiazolinium enolate 9 derived by C(5)-C(6) ring opening of the formylpenicillanate 8, in a similar manner to that of the thiazolothiazinones 6[3]. The stereochemical aspects of these processes, along with those involved in the initial formation of 8 via the diazo adduct 7 are however uncertain at the present time.

This seems to be the first report of the formation of 6-formylpenicillanates from a diazopenicillanate, although such reactions are well documented for diazoalkanes.[8] Furthermore, the novel rearrangements described, further extend the general susceptibility of penicillanates bearing carbon-heteroatom double bonds at C(6) towards C(5)-C(6) cleavage reactions.

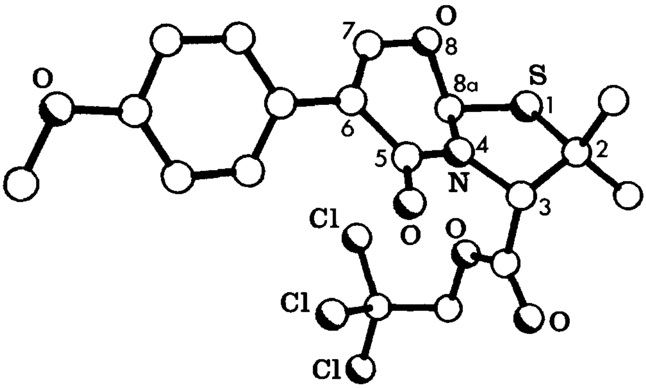
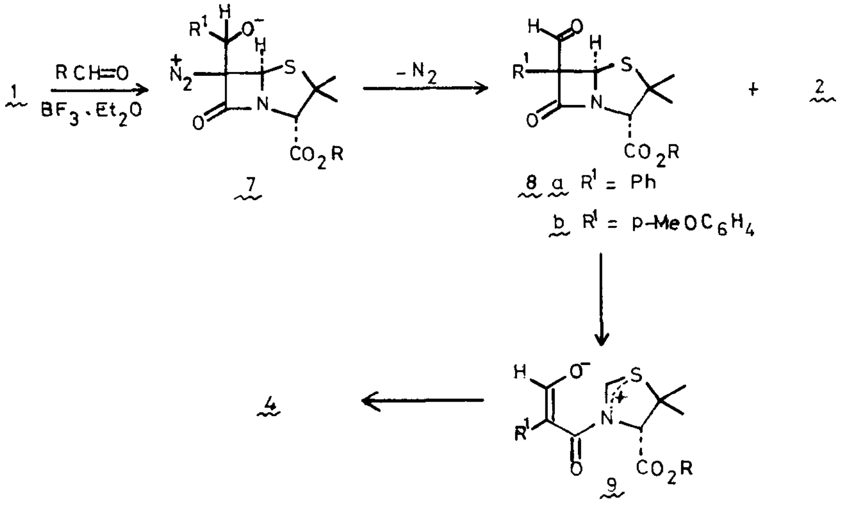


Figure. The molecular structure of 4c.
Selected bond distances: S(1)-C(2) 1.850(4), S(1)-C(8a) 1.795(4), C(2)-C(3) 1544(5), C(3)-N(4) 1.448(5), N(4)-C(5) 1.363(5), C(5)-O(5) 1.216(5), C(5)-C(6) 1.481(6), C(6)-C(7) 1.330(6), C(7)-O(8) 1.361(5), O(8)-C(8a) 1.430(5), N(4)-C(8a) 1.438(5) Å.



Scheme

Acknowledgements

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References, Notes and Spectral Data

1. J.C. Sheehan, E. Chacko, Y.S. Lo, D.R. Ponzi, and E. Sato, J. Org. Chem., 1978, **43**, 4856.
2. J.C. Sheehan, K. Nakajima, and E. Chacko, Heterocycles, 1979, **13**, 227.
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5. **4a**: m.p. 98-99°, ν_{max}(CHCl$_3$) 1760 and 1675 cm^{-1}; ^{1}H δ(CDCl$_3$) 1.57 and 1.82 (each 3H, s, CMe$_2$), 4.80 (2H, s, CH$_2$), 4.98 (1H, s, H-3), 6.85 (1H, s, H-8a), 7.2-7.6 (6H, m, aromatic and H-7); ^{13}C δ(CDCl$_3$) inter alia 95.44 (C-8a), 153.63 (C-7), 160.73 (C-5) and 167.09 (ester C=O); m/e 434.9861 (M$^+$).
   4c: m.p. 140-1°, ν_{max}(CHCl$_3$) 1760 and 1660 cm^{-1}; ^{1}H δ(CDCl$_3$) 1.58 and 1.85 (each 3H, s,

CMe$_2$), 3.82 (3H, s, OMe), 4.81 (2H, s, CH$_2$), 4.99 (1H, s, 3-H), 6.84 (1H, s, 8a-H), 6.90 and 7.42 (4H, ABq, aromatic), 7.29 (1H, s, 7-H); ^{13}C δ(CDCl$_3$) *inter alia* 95.34 (C-8a), 152.81 (C-7), 161.04 (C-5), 167.20 (ester C=O); m/e 464.9970 (M$^+$).
Products **4b** and **4d** showed satisfactory analytical and spectroscopic data. Structures **4b** and **4c** represent corrected assignments for the products reported[2] as **5b** and **5c**. Data for the furfural product was consistent with **4a-4c** and excluded the structure **5d**.

6. **8a**: m.p. 112-4°; ν_{max}(CHCl$_3$) 1790, 1765 and 1720 cm^{-1}; ^{1}H δ(CDCl$_3$) 1.58 and 1.68 (each 3H, s, CMe$_2$), 4.61 (1H, s, 3-H), 4.74 (2H, s, CH$_2$), 5.63 (1H, s, 5-H), 7.4 (5H, s, aromatic), 9.55 (1H, s, CH=O).
8b: m.p. 106-7°, ν_{max}(CHCl$_3$), 1785, 1765 and 1720 cm^{-1}; ^{1}H δ(CDCl$_3$) 1.58 and 1.67 (each 3H, s, CMe$_2$), 3.80 (3H, s, OMe), 4.61 (1H, s, 3-H), 4.76 (2H, s, CH$_2$), 5.59 (1H, s, H-5), 6.90 and 7.40 (4H, ABq, aromatic), 9.52 (1H, s, CH=O); m/e 465 (M$^+$).

7. *Crystal Data* (**4c**), $C_{18}H_{18}O_5NSCl_3$, M = 466.8 orthorhombic, a = 6.502(1), b = 17.838(2), c = 18.036(2) Å, U = 2092 Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.49 g cm^{-3}. 1565 independent observed reflections [$|F_o|>3\sigma(|F_o|)$, $\theta \leqslant 58°$] were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) and using ω scans. The structure was solved by direct methods and refined anisotropically to give R = 0.036, R_w = 0.039. Refinement of a free variable η that multiplies all f'' converged to a value of -1.05(6) indicating the initial coordinate set to be of the wrong chirality. The figure shows the correct absolute configuration. Tables of atomic co-ordinates, bond lengths and bond angles have been deposited with the Cambridge Crystallographic Data Centre.

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