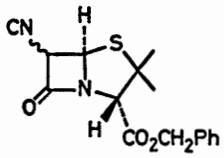
Reactions of Benzyl 6-Isocyanopenicillanate with Thiocarbonyl Reagents. Novel rearrangements to 2,3-Dihydrothiazolo[2,3-*b*][1,3]-thiazin-5-ones *via* Penam C(5)–C(6) Bond Cleavage. *X*-Ray Crystal Structure and Absolute Configuration of Two Rearrangement Products

D. Ivor John,*[a] Nicholas D. Tyrrell,[a] Eric J. Thomas,*[b] Peter H. Bentley,[c] and David J. Williams*[d]

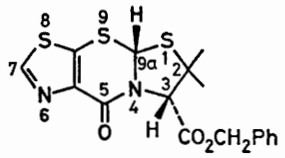
[a] *Department of Chemistry, University of London King's College, Strand, London, WC2R 2LS, U.K.*
[b] *The Dyson Perrins Laboratory, South Parks Road, Oxford, OX1 3QY, U.K.*
[c] *Beecham Pharmaceuticals Research Division, Brockham Park, Betchworth, Surrey, RH3 3AJ, U.K.*
[d] *Chemical Crystallography Laboratory, Imperial College of Science and Technology, South Kensington, London, SW7 2AY, U.K.*

Base-promoted reactions of benzyl 6-isocyanopenicillanate with CS_2, with CS_2–MeI, and with PhNCS, proceed *via* C(5)–C(6) bond cleavage to give pairs of diastereoisomers; the structures of two of these diastereoisomers were established by *X*-ray crystallography.

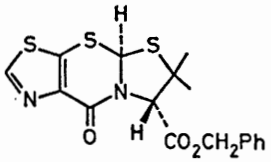
Rearrangement reactions of the penicillin nucleus which involve C(5)–C(6) bond cleavage have rarely been reported. Stoodley[1] has suggested some circumstances under which such cleavage may occur, and has described the reaction of lead tetra-acetate with benzyl 6-aminopenicillanate as a possible example. C(5)–C(6) bond cleavage has also been invoked to explain the t-butyl hypochlorite-induced fragmentation of benzyl penicillin sulphoxide methyl ester,[2] and is involved in



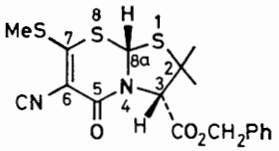
(1)



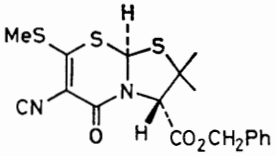
(2)



(3)



(4)



(5)

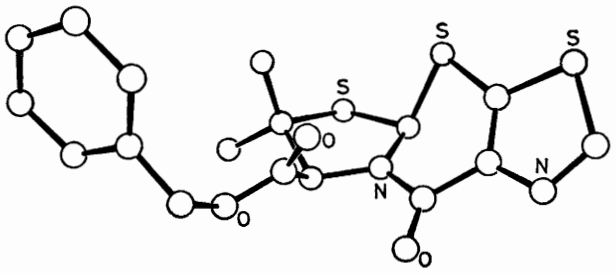


Figure 1. Molecular structure of (**2**).

the formation of methyl benzylpenillonate.[3] We now report a series of reactions which unequivocally involve rearrangement of the penicillanate nucleus by initial cleavage of the C(5)–C(6) bond.

As part of our work on the chemistry of 6-isocyanopenicillanates,[4,5] we studied the reaction of benzyl isocyanopenicillanate (**1**) with CS_2 and base.[6] Thus, isocyanopenicillanate (**1**) was treated with anhydrous K_2CO_3 and CS_2 in *N*,*N*-dimethylformamide (DMF) at room temperature. Two products were formed in a *ca.* 1 : 1 ratio (t.l.c.), and were separated by column chromatography on silica which gave the faster moving component as an oil (23% yield), and the slower moving component as a pale yellow solid (35% yield, m.p. 132—133 °C). Chemical and mass spectroscopic analysis indicated that the products were isomers, formula $C_{17}H_{16}N_2O_3S_3$, but structures could not be unambiguously assigned. However, an *X*-ray structure determination for the major crystalline isomer revealed (Figure 1) that it was the novel tricycle, benzyl 2,3-dihydro-2,2-dimethyl-5*H*,9a*H*-bisthiazolo[2,3-*b*:4′,5′-*e*][1,3]-thiazin-5-one-3-carboxylate (**2**), having the 3*R*, 9a*S* configuration. Spectroscopic assignments were then made as follows: ν_{max} (KBr) 1755 (ester CO) and 1660 (amide CO) cm^{-1}; δ ($CDCl_3$) 1.49 and 1.59 (each 3H, s, CMe_2), 4.78 (1H, s, $CHCO_2R$), 5.17 (2H, s, CH_2Ph), 6.54 (1H, s, SC*H*S), 7.28 (5H, s, *Ph*), and 8.65 (1H, s, NC*H*S). The non-crystalline isomer was identified as the epimeric thiazinone (**3**) on the basis of the following data; ν_{max} (KBr) 1745 (ester CO) and 1670 (amide CO) cm^{-1}; δ ($CDCl_3$) 1.40 and 1.83 (each 3H, s, CMe_2), 4.88 (1H, s, $CHCO_2R$), 5.19 and 5.24 (each 1H, d, *J* 10 Hz, CH_2Ph), 6.73 (1H, s, SC*H*S), 7.33 (5H, s, *Ph*), and 8.69 (1H, s, NC*H*S). When the crystalline *cis*-diastereoisomer (**2**) was heated under reflux in solution in toluene, epimerization occurred, and a mixture of the *cis*-isomer (**2**) and the *trans*-isomer (**3**) was obtained, (**2**):(**3**) = 1:9 after 5 h.

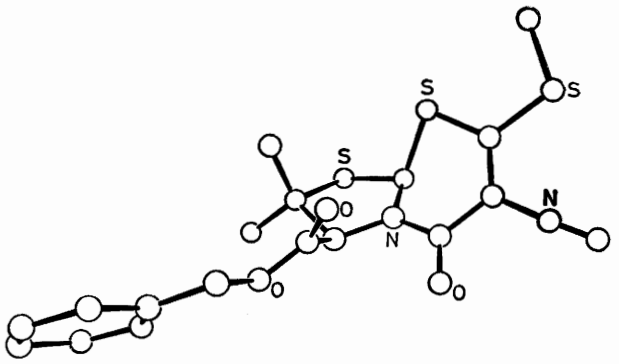


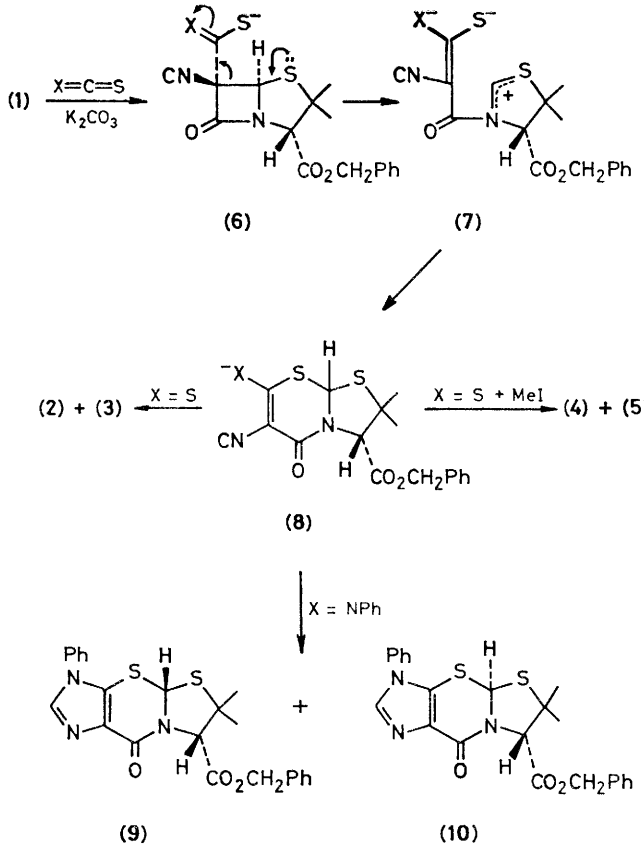
Figure 2. Molecular structure of (**4**).

In an attempt to methylate any intermediate dithiocarboxylate ion (**6**; X = S), the reaction of isocyanopenicillanate (**1**) with CS_2 and K_2CO_3 was repeated in the presence of an excess of methyl iodide. In this case two new products were obtained, and were separated by column chromatography on silica. This separation gave an oil (14% yield), and a slower moving crystalline solid [18% yield, m.p. 152—154 °C (decomp.)]. Chemical and mass spectroscopic data again showed these two products to be isomers, and their i.r. spectra showed the presence of the isonitrile function, but no β-lactam. *X*-Ray crystallography was used to establish unambiguously the structure of the crystalline isomer as benzyl 2,3-dihydro-2,2-dimethyl-6-isocyano-7-methylthio-5-oxo-5*H*,8a*H*-thiazolo-[2,3-*b*][1,3]thiazin-3-carboxylate (**4**) with the 3*R*, 8a*S* configuration (see Figure 2). The oily isomer was therefore identified as the thiazinone isonitrile (**5**) with the 3*R*, 8a*R* configuration. Attempts to interconvert isomers (**4**) and (**5**) in refluxing toluene were thwarted by accompanying decomposition.

Crystal data: crystals of (**2**) are tetragonal, space group $P4_32_12$, $a = 8.122(1)$, $c = 56.25(1)$ Å; $U = 3711$ Å^3, $Z = 8$. Crystals of (**4**) are monoclinic, space group $P2_1$, $a = 9.667(1)$, $b = 8.766(1)$, $c = 11.584(1)$ Å; $\beta = 104.81(1)°$, $U = 952$ Å^3, $Z = 2$. Data for both compounds were measured on a diffractometer using Cu-K_α radiation. For (**2**), 1669 independent reflections ($\theta \leqslant 60°$) were measured and, for (**4**), 1971 ($\theta \leqslant 70°$). The number of reflections classed as unobserved were 199 and 20 for (**2**) and (**4**) respectively, $I < 2.58\sigma(I)$. Both structures were solved by direct methods and refined anisotropically to give current *R* values of 0.050 (**2**) and 0.054 for (**4**).† For both structures the absolute configurations were determined from the anomalous scattering due to the sulphur atoms. [For (**2**), $R^+ = 0.050$, *cf.* $R^- = 0.055$; for (**4**), $R^+ = 0.054$, *cf.* $R^- = 0.057$.]‡

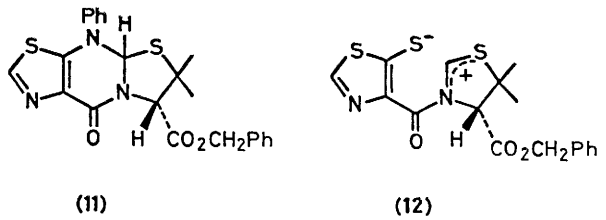
† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

‡ The 3*R* configuration in (**2**) and (**4**) is consistent with that of the original penicillanate (**1**). The carbon–isonitrile bond system of (**4**) is essentially linear with C–N–C angle = 179.1(8)°, and bond lengths, C–N = 1.40(1), and N≡C = 1.14(1) Å. The isonitrile bond length is in close agreement with that found earlier (ref. 4).



Scheme 1

The formation of both pairs of epimers (**2**) and (**3**), and (**4**) and (**5**) can be explained (Scheme 1) in terms of the initial formation of the dithiocarboxylate anion (**6**; X = S) followed by C(5)–C(6) bond cleavage of the penicillanate nucleus to provide the stabilized thiazoline cation (**7**; X = S) which then recyclizes to the thiazolothiazinone intermediate (**8**; X = S). The tricyclic epimers (**2**) and (**3**) would then arise by further ring closure of the thiolate anion of (**8**; X = S) at the isonitrile function, while, in turn, the bicyclic epimers (**4**) and (**5**) would be formed by S-methylation of (**8**; X = S). Since both epimers are produced in each reaction, it seems unlikely that the thiazolothiazinone intermediate (**8**; X = S) is formed directly from the dithiocarboxylate (**6**; X = S) by a concerted process.



Base-promoted reactions of isonitrile (**1**) with other heterocumulenes were also briefly examined. Thus, treatment of isonitrile (**1**) with an excess of phenylisothiocyanate and anhydrous K_2CO_3, in dry DMF led to the formation of two products isolated by repeated chromatography on silica and identified as the *cis*- and *trans*-diastereoisomers (**9**) and (**10**), isolated in 42% and 3% yields, respectively. The very close spectroscopic relationship of these epimers with the corresponding epimers from the CS_2 reactions allowed both the assignment of configuration, and the exclusion of an alternative structural possibility (**11**). Owing to the extreme insolubility of the minor *trans*-isomer (**10**), a definitive study of the thermal equilibration of (**9**) and (**10**) was not possible.

The thermal isomerisation of the tricyclic *cis*-isomer (**2**) is thought to proceed *via* intermediate (**12**) formed by cleavage of the S–C(9a) bond; however, attempts to trap this intermediate have been unsuccessful to date.

We thank the S.R.C. for a CASE Award (to N. D. T.) and Beecham Pharmaceuticals for their generous support.

Received, 7th October 1981; Com. 1187

References

1 R. J. Stoodley, *Tetrahedron*, 1975, 2321.
2 J. Nakano, H. Kanda, Y. Nakamura, M. Nakata, and M. Tomita, *Tetrahedron Lett.*, 1976, 2797.
3 R. Sharma and R. J. Stoodley, *J. Chem. Soc., Perkin Trans.* 1, 1980, 2001.
4 P. H. Bentley, J. P. Clayton, M. O. Boles, and R. J. Girven, *J. Chem. Soc., Perkin Trans.* 1, 1979, 2455.
5 D. I. John, E. J. Thomas, and N. D. Tyrrell, *J. Chem. Soc., Chem. Commun.*, 1979, 345.
6 U. Schöllkopf, P.-H. Porsch, and E. Blume, *Liebigs Ann. Chem.*, 1976, 2122.