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FORMATION OF β-LACTAMS FROM 3-PHENYLTHIOPROPIONAMIDE DERIVATIVES

A POSSIBLE MODEL FOR PENICILLIN BIOSYNTHESIS

ATHELSTAN L. J. BECKWITH and CHRISTOPHER J. EASTON
Research School of Chemistry, Australian National University, Canberra, A.C.T., Australia

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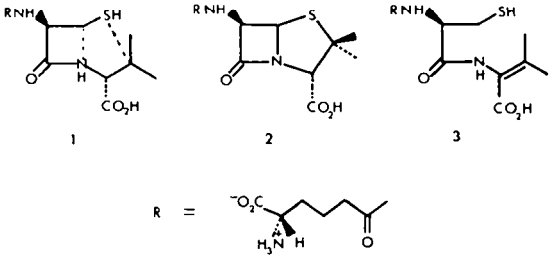
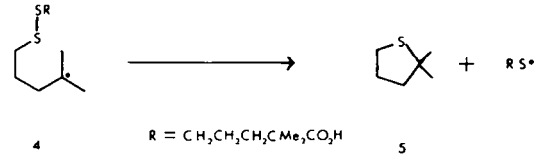
Abstract—The Cu-catalysed reaction of the substituted 3-phenylthiopropianamide (**10a**) with di-t-butyl peroxide gives the β-lactam (**14a**) *via* oxidative cyclisation of the α-thioalkyl radical (**11a**). Similar reactions of the propionamides (**10a**, **10b**) with t-butyl perbenzoate give benzoates (**15**, **17**) which can be readily converted into the β-lactams (**14a**, **14b**), but neither β-lactams nor benzoates can be obtained from the thiazepines (**23a**, **23b**). Dimethyl disulfide is benzoyloxylated on treatment with t-butyl perbenzoate. The relevance of these results to penicillin biosynthesis is discussed.

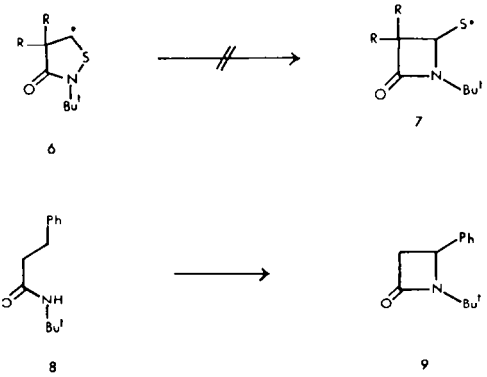
Despite intensive investigation[1] the intimate details of the biosynthesis of penicillin and related β-lactam antibiotics have not yet been elucidated. Although it is generally accepted that the Arnstein tripeptide, δ (L-α-aminoadipyl)-L-cysteinyl-D-valine (**1**), is a precursor of isopenicillin N (**2**),[1-3] the mechanism of the conversion *in vivo* of the former into the latter remains obscure. Labelling studies[4] and related experiments[5] have revealed that the ring closures affording the β-lactam and thiazolidine moieties occur with retention of configuration at the appropriate C atoms, and do not involve the intermediacy of unsaturated compounds (e.g. **3**). Most attempts to detect stable intermediates *in vivo* on the pathway from **1** to **2** have been unsuccessful and evidence suggesting that C–N bond formation precedes C–S bond formation[3] has not been confirmed.[6]



Each of the ring closures involved in the conversion of **1** into **2** requires the loss of two H atoms. The suggestion[7,8] that these oxidative cyclisations are homolytic processes seems plausible in the light of evidence that enzymatic hydroxylation[9] and other biological oxidations[10] proceed *via* free-radical intermediates. The fact that the penicillin synthetase enzyme is dependent on Fe^{2+} and oxygen[1] gives further credence to this hypothesis.

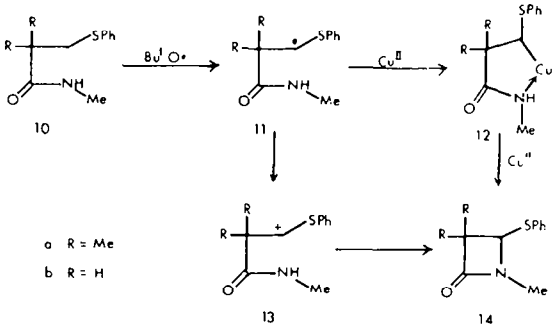


An adequate model (**4**→**5**) for formation of the thiazolidine ring of penicillin by an intramolecular S_H2 reaction of a carbon centred radical with an S–S bond has already been described.[9] Attempts to provide *in vitro* examples of free-radical processes leading to β-lactams by C–N bond formation have been somewhat less successful. Appropriate model experiments[8] showed that the putative radical rearrangement (**6**→**7**) does not occur. However, treatment of the amide (**8**) with di-t-butyl peroxide and a Cu catalyst, reagents expected to generate radical intermediates,[11] gave the lactam (**9**), albeit in very small yield.[12] In the present work, which was independently conceived and initiated, we have conducted similar experiments with suitable S containing substrates, and have shown that arylthio-substituted β-lactams can be generated either directly or indirectly from appropriate acyclic amides (e.g. **10a**) but not from thiazepines (e.g. **23a**).



Our experiments were based on the knowledge that α-thioalkyl radicals (e.g. **11a**) can be readily generated by H-atom transfer from the corresponding sulfide (e.g. **10a**) to t-butoxy radicals,[13-15] and on the hypothesis that interaction of such radicals (**11a**) with cupric species should afford the β-lactam (**14a**) either by intramolecular ligand transfer involving intermediates such as **12a**, or *via* the cation (**13a**) generated by electron transfer. It is noteworthy that the Cu-catalysed reactions of simple dialkyl sulfides with t-butyl perbenzoate afford moderate

yields of α-benzoyloxy sulfides.[11] However, the mechanistic details of such reactions have not yet been elucidated.



RESULTS AND DISCUSSION

The propionamide derivative (**10a**), chosen as substrate for our initial experiments because the presence of the two Me substituents precludes side reactions involving deprotonation at C-2, was readily prepared from chloropivalic acid by reaction with thiophenol and potassium fluoride in dimethylformamide followed by amide formation. When **10a** was heated for 6 hr in boiling benzene with t-butyl perbenzoate and a catalytic amount of cuprous bromide, the major product (71%) was the benzoate (**15**) but the required β-lactam (**14a**) was also obtained in small yield. In the absence of cuprous bromide the reaction proceeded more slowly and after 18 hr afforded only the benzoate (**15**; 37%) and starting material (54%). No β-lactam (**14a**) was detected.

15 R' = Me, R'' = OCOPh
16 R' = Me, R'' = Br
17 R' = H, R'' = OCOPh
18 R' = H, R'' = Br

19

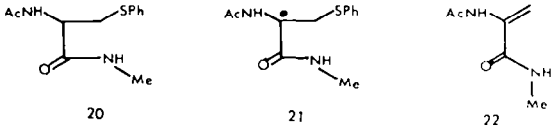
The β-lactam (**14a**) was obtained in good yield when the benzoate (**15**) was treated consecutively with hydrogen bromide and with potassium amide in liquid ammonia. This route to **14a** involves formation of the bromo-compound (**16**) followed, presumably, by intramolecular nucleophilic displacement of bromide.

The predominant formation of the benzoate (**15**) in the Cu-catalysed reaction of **11a** with t-butyl perbenzoate suggests that the benzoate ion competes effectively with the amide function either as a necleophile towards the positive centre of **13a** or as a ligand to copper in ligand transfer reactions of **11a**. Accordingly, the reaction was repeated with di-t-butyl peroxide as the source of t-butoxy radicals. As expected (because di-t-butyl peroxide is less susceptible than t-butyl perbenzoate towards reduction by cuprous species) this reaction was much slower and a higher temperature was required. At low conversion (38%) only the β-lactam (**14a**) was formed in 18% yield (47%, based on unrecovered starting material). However, attempts to improve the yield by increasing the conversion afforded complex mixtures, presumably because **14a** is more susceptible than the starting material (**10a**) towards attack by t-butoxy radicals.[16] Similar yields of **14a** were obtained when the reaction was conducted at ambient temperature under UV irradiation.

Heating of the amide (**10b**) bearing no substituents at C-2 with t-butyl perbenzoate and cuprous bromide afforded the benzoate (**17**) in good yield (>70%). Some starting material was recovered but neither the β-lactam (**14b**) nor the unsaturated amide (**19**) could be detected. Treatment of the benzoate (**17**), first with hydrogen bromide, then with potassium amide, gave **14b**, an authentic specimen of which was prepared by an unambiguous route. Interestingly, the reaction involving potassium amide gave no detectable amount of the unsaturated amide (**19**). Presumably, this indicates that deprotonation of the bromoamide (**18**) with strong base is confined to the amide function, and that the resultant ion undergoes very rapid ring closure by intramolecular nucleophilic displacement.

When the amide (**10b**) was treated with di-t-butyl peroxide and cupric bromide in naphthalene at 130° no β-lactam (**14b**) could be detected. The only product isolated was the unsaturated amide (**19**) which was assigned the *cis* configuration because of the magnitude of the vicinal coupling of the olefinic protons.[8]† Similarly, UV irradiation of **10b** with cupric bromide in di-t-butyl peroxide gave only the unsaturated amide (**19**).

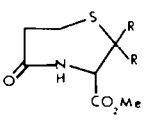
Attempts to generate a β-lactam from the acetylamino compound (**20**), a good analogue of the Arnstein tripeptide (**1**), were unsuccessful. Treatment of **20** in the usual way with di-t-butyl peroxide or t-butyl perbenzoate and a Cu salt gave complex mixtures in which neither β-lactam nor benzoyloxylated products could be detected. However, when the reaction of **20** with t-butyl perbenzoate and cuprous bromide was run to low conversion it gave a single product which was isolated in slightly impure form. Its spectral properties support its formulation as the acrylamide derivative (**22**) formed, presumably, by loss of phenylthio radical from the radical (**21**) generated by attack of t-butoxy radical at C-2 of **20**.



In an attempt to mimic the generation of the β-lactam ring in a hypothetical biosynthetic process involving C–S bond formation prior to C–N bond formation, the thiazepines (**23a** and **23b**) were treated in the usual way with di-t-butyl peroxide or t-butyl perbenzoate. Both compounds were considerably less reactive than the acyclic sulfides (**10a** and **10b**) towards H-abstraction by t-butoxy radicals. Thus, when either was heated with 2.5 molar equiva of t-butyl perbenzoate and cuprous bromide in benzene until <10% of the perester remained, the thiazepine could be recovered in >90% yield. The major product was methyl benzoate. This indicates that β-fission of t-butoxy radicals, $Bu^tO\cdot \rightarrow MeCOMe + Me\cdot$, competes effectively with H-abstraction from **23a** or **23b**. We are unable to provide an

†In the absence of the other double bond isomer this assignment is based on tenuous evidence.

explanation for the low reactivity of the thiazepines towards attack by t-butoxy radicals, since inspection of models reveals no steric or stereo-electronic inhibition of the reaction. A quantitative examination of reactivity in these and related systems appears to be warranted.



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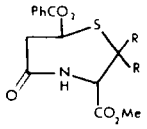

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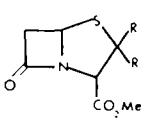

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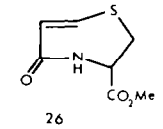
a R = H
b R = Me

When either of the thiazepines **23a** or **23b** was heated, or irradiated with UV light, in the presence of a very large excess of di-t-butyl peroxide or t-butyl perbenzoate and a Cu salt catalyst, a complex mixture of products was formed which contained neither the benzoate (**24**) nor the β-lactam (**25**), an authentic sample of which was prepared from 6-aminopenicillanic acid. However, from reactions of the thiazepine (**23a**) it was possible to isolate small amounts of the two olefins (**26** and **27**).



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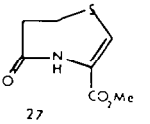

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Finally, we examined the reaction of dimethyl disulfide, MeSSMe, with t-butyl perbenzoate. The reaction in the absence of a Cu salt proceeded slowly in boiling benzene and afforded the benzoate, $PhCO_2CH_2SSMe$, in small yield (1.5%). Addition of cuprous bromide had little effect upon either the rate or the outcome of the reaction. Treatment of the benzoate with hydrogen bromide in the usual way gave the bromosulfide, $BrCH_2SMe$, after chromatography of the crude product. However, NMR examination of the mixture indicated that the primary product is the bromo-disulfide, $BrCH_2SMe$, which undergoes facile rearrangement during the course of the reaction and subsequent work-up.

Mechanism

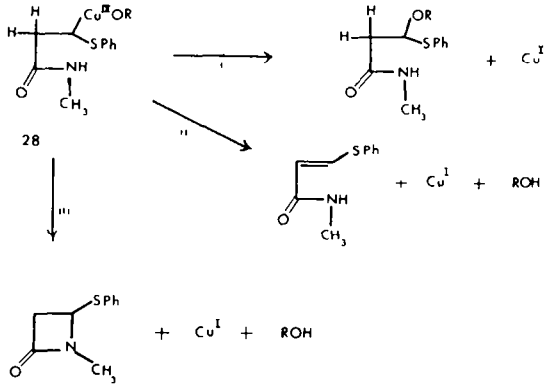
Most of the results described above accord well with previous observations[13,14] that H-atom abstraction by t-butoxy radicals from thioethers occurs preferentially at positions adjacent to the S atom, presumably because of the stabilisation of the resultant radicals through interaction of the unpaired electron with sulphur lone pairs. The only substrate which did not conform to this pattern was that **20** in which H-atom abstraction from the position adjacent to both N and C=O affords a capto-dative radical[17] (**21**) stabilised by extended conjugation over both groups.

There is no firm information available concerning the mechanisms of the reactions whereby the α-thioalkyl radicals generated in the first step are converted into the final products. It has been suggested[16] that outer-sphere one-electron oxidation by cupric species affords carbocations (e.g. **13**) which then undergo coupling with suitable nucleophiles. However, if such a mechanism applies to all our substrates it is difficult to see why deprotonation to afford the unsaturated compound, a process which should be favoured for carbocations containing a β-amido function (e.g. **13b**), occurs in some cases, but not in others. For example the Cu-catalysed reaction of **10b** with di-t-butyl peroxide gave only the unsaturated amide (**19**), but the latter (**19**) could not be detected when t-butyl perbenzoate was used. Conversely, the thiazepine (**23a**) when treated with the perester and a Cu salt gave only the olefinic compounds (**26** and **27**).

It is well known that some radicals undergo direct ligand transfer with suitable cupric species.[18] Thus, the formation of benzoates in our experiments could be envizaged as involving S_H2 attack of the radical on cupric benzoate:

$$-\dot{S}CHR + Cu^{II}OCOPh \rightarrow -SCHROCOPh + Cu^{I}.$$

However, the formation of the β-lactam (**14a**) by a similar intramolecular process would require *either* that t-butoxy radicals react only with those substrate molecules already complexed to Cu, *or* that the radical (**11a**) forms a Cu-amide complex more rapidly than it undergoes any other reaction. We consider both hypotheses to be unlikely.



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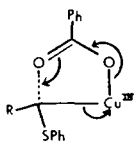
Simple alkyl radicals react with cupric species by coupling to give organo-Cu (III) complexes.[18,19] Our results can be accomodated by mechanisms involving the intermediacy of such species. The putative Cu(III) intermediate (**28**) generated from **11a** or **11b** should be potentially capable of undergoing three distinct reactions: (i) displacement of Cu by the RO (R=Bu^t or PhCO) group either by intermolecular nucleophilic substitution,

$$RO^- + R'Cu^{III}OR \rightarrow ROR' + Cu^{I} + OR^-,$$

or by intramolecular ligand transfer, $R'Cu^{III}OR \rightarrow R'OR + Cu^{I}$; (ii) deprotonation and elimination to afford an olefin; (iii) intramolecular displacement of Cu to give the lactam (**14a**), either by direct nucleophilic attack or *via* formation of the cyclic complex **12a**. The relative rates of theses three competing processes should depend in a predictable manner on the nature of the substrate and the reaction conditions.

When benzoate is present, i.e when t-butyl perbenzoate is employed, reactions of type (i) are favoured both because benzoate ion is a relatively good nucleophile and because cyclic mechanisms (e.g. **29**) are available.

In reactions involving di-t-butyl peroxide the intermediate (**28**, R=Bu^t) preferentially undergoes reaction (ii)



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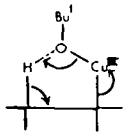

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presumably because t-butoxide is a strong protic base or because of the accessibility of a cyclic process (e.g. **30**). We prefer the latter since the formation of β-lactams (e.g. **14b**) by direct treatment of bromo-amides (e.g. **18**) with strong base suggests that the intermediate (**28**) should undergo preferential deprotonation at the amide function.

The ring-closure (iii) appears to be the slowest of all the processes available to the Cu(III) complexes in our reactions, presumably because of the strain-energy engendered in the formation of the β-lactam ring. It is important, therefore, only when benzoate is absent and when deprotonation is prevented by substitution of the position adjacent to the CO group.

Previous workers[20] have suggested that reactions of thioethers with diacyl peroxides or peresters might involve radical and/or ionic intermediates. The fact that we were unable to isolate products usually associated with the ionic route from uncatalysed perester reactions suggests that formation of benzoyloxylated products (e.g. **17** from **10b**) involves radical intermediates. The chain propagation step could proceed either by an S_H2 mechanism,

$$ArS\dot{C}HR + Bu^tOOCOPh \rightarrow ArSCHROCOPh + Bu^tO^{\cdot},$$

or by electron transfer,

$$ArS\dot{C}HR + Bu^tOOCOPh \rightarrow Ar\overset{+}{C}HR + Bu^tO^{\cdot} + PhCO_2.$$

We prefer the former since the latter would be expected to afford some unsaturated products.

CONCLUSION

Our experiments show that suitable β-arylthio-alkanecarboxamides can be converted directly into β-lactams by treatment with di-t-butyl peroxide and a Cu salt catalyst. The same transformation can be effected in better overall yield and greater generality by the indirect route involving consecutive treatment with hydrogen bromide and with sodium amide of the benzoates obtained when t-butyl perbenozoate is employed as the radical precursor. Both routes offer scope for synthetic exploitation.

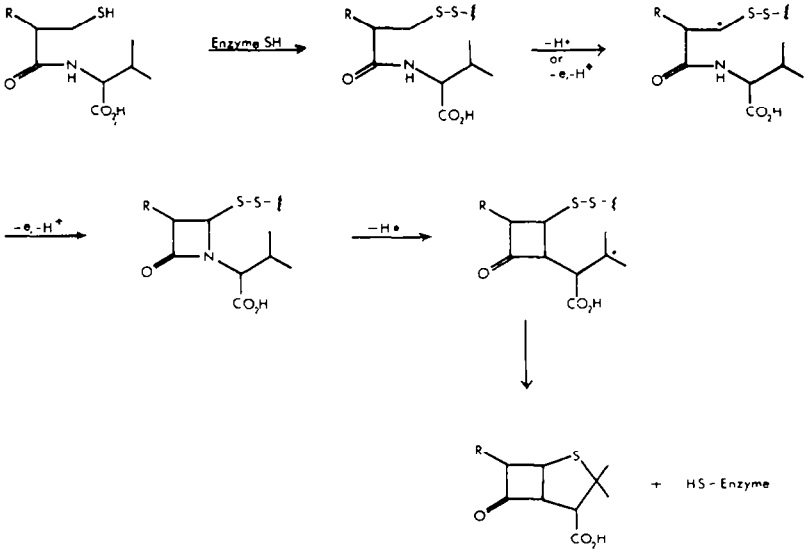
The observation that β-lactams can be generated by a direct oxidative cyclisation of suitable amides gives further credence to the suggestion[8,12] that the biosynthesis of β-lactam antibiotics might involve radical intermediates. Indeed, it now appears that the biosynthetic pathway set out in Scheme 1 is consistent with all the evidence available from labelling and other biosynthetic studies, and involves plausible oxidative ring closures for which appropriate *in vitro* models are available.

EXPERIMENTAL

M.ps were measured on a Reichert hot-stage melting apparatus and are uncorrected. Microanalyses were performed by the Australian National University Microanalytical Unit. IR spectra of neat liquids or of nujol mulls of solids were measured on a Perkin–Elmer 683 spectrophotometer. NMR spectra were measured relative to TMS as internal standard on a Jeol Minimar spectrometer operating at 100 MHz or on a Joel JNM-PMX 60 spectrometer operating at 60 MHz. Mass spectra were measured at 70 eV on an AEI MS902 spectrometer. Accurate mass measurements were carried out with heptacosane as a reference compound. Distillations were carried out on a Buchi GKR-50 glass oven and b.ps are the temperatures required for distillation. UV irradiation was achieved with a G.E.C. 250-W mercury lamp. Solvents were purified by standard procedures. Light petroleum refers to the fraction b.p. 40–60°. Flash chromatography was performed on Merck Kieselgel 60 (0.04–0.063 mm).

2,2-Dimethyl-3-(phenylthio)propionic acid

A mixture of 3-chloro-2,2-dimethylpropionic acid[21] (2.73 g, 20.0 mmol), KF (1.36 g, 23.4 mmol) and thiophenol (4.44 g, 40 mmol) was heated in dimethylformamide (20 ml) under N_2 at 120–130° for 12 hr, then poured into cold water (100 ml). The resultant ppt was dissolved in 1N NaOH, washed with CH_2Cl_2, and reprecipitated with dil HCl. Crystallisation from aqueous EtOH afforded colourless needles of 2,2-dimethyl-3-(phenylthio)propionic acid (3.02 g, 72%), m.p. 116–118° (lit.[22] m.p. 116–117°).



N-2,2-Trimethyl-3-(phenylthio)propionamide (**10a**)

A mixture of 2,2-dimethyl-3-(phenylthio)propionic acid (3.00 g, 14.4 mmol) and $SOCl_2$ (1.25 ml) was heated at 80° for 2 hr then dissolved in CH_2Cl_2 (30 ml) and added dropwise over 1 hr to a soln of 40% NH_2MeAq (30 ml) at −5–−10°. After the mixture had been stirred for 2 hr at 0°, water (30 ml) was added, and the organic layer was separated, washed with water, and with 5N H_2SO_4 and water, then dried and concentrated. Crystallisation of the residual oil from EtOAc-light petroleum gave *N-2,2-trimethyl-3-(phenylthio)propionamide* **10a** (2.46 g, 77%) as needles, m.p. 61.5–62.0°. (Found: C, 64.24; H, 7.55; N, 6.49; S, 14.12. $C_{12}H_{17}NOS$ requires: C, 64.54; H, 7.67; N, 6.27; S, 14.36%), δ ($CDCl_3$) 1.30 [6H, s, $C(CH_3)_2$], 2.70 (3H, d, *J* 5 Hz, NCH_3), 3.15 (2H, s, CH_2), 6.0 (1H, b, NH), 7.1–7.5 (5H, m, Ar), ν_{max} 3342, 1643, 1555 cm^{-1}, *m/e* 223 (M^+, 70%), 165 (13%), 123 (88%), 114 (100%).

The reactions of N-2,2-*trimethyl*-3-(*phenylthio*)*propionamide* (**10a**) *with t-butyl perbenzoate*

(a) A mixture of **10a** (2.23 g, 0.01 mol), t-butyl perbenzoate (2.13 g, 0.012 mol), cuprous bromide (*ca* 10 mg) and dry benzene (50 ml) under N_2 was heated under reflux for 6 hr, then cooled, washed with $Na_2S_2O_5$ aq and water, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue in EtOAc-CH_2Cl_2 (20:80) afforded an oil which was distilled to give *1,3,3-trimethyl-4-phenylthioazetidin-2-one* **14a** (86 mg, 4%), b.p. 65–70° at 0.2 mm Hg (GKR), δ ($CDCl_3$) 1.33 (3H, s, C-CH_3), 1.37 (3H, s, C-CH_3), 2.76 (3H, s, NCH_3), 4.64 (1H, s, CH), 7.1–7.5 (5H, m, Ar), ν_{max} 1752 cm^{-1}, *m/e* 221 (M^+, 5%), 164 (M^+-CH_3NCO, 9%), 112 (M^+-SC_6H_5, 100%), *m/e* 22.0879 (M^+) (calc for $C_{12}H_{15}NOS$ (M^+) *m/e* 221.0874).

Continued elution of the column afforded *3-benzoyloxy-N-2,2-trimethyl-3-(phenylthio-propionamide* (**15**) which crystallised from EtOH–light petroleum as colourless plates (2.42 g, 71%), m.p. 134–136° dec, δ ($CDCl_3$) 1.44 [6H, s, $C(CH_3)_2$], 2.72 (3H, d, *J* 5 Hz, NCH_3), 6.0 (1H, b, NH), 6.52 (1H, s, CH), 7.0–8.0 (10H, m, Ar), ν_{max} 3357, 1717, 1633, 1538 cm^{-1}, *m/e* 343 (M^+, 1%), 234 (M^+-SC_6H_5, 20%), 222 (M^+-$OCOC_6H_5$, 2%), 105 (C_6H_5CO, 100%), *m/e* 343.1228 (M^+) (Calc for $C_{19}H_{21}NO_3S$ (M^+) *m/e* 343.1242). Further elution of the column afforded the starting amide **10a** (0.17 g, 8%).

(b) When the amide (**10a**) and the perester were heated without a Cu salt in benzene under reflux for 18 hr **15** (37%) was isolated and **10a** (54%) was recovered. The lactam (**14a**) could not be detected by TLC.

Preparation of 1,3,3-*trimethyl*-4-*phenylthioazetidin*-2-*one* (**14a**) *from* **15**

A soln of **15** (0.45 g, 1.3 mmol) in dry CH_2Cl_2 (10 ml) was added dropwise with stirring to an ice-cold soln of dry HBr in CH_2Cl_2 (50 ml). After the addition the soln was allowed to stand for 2 hr at 0–5°. Subsequent removal of the solvent afforded a pale yellow solid which was dissolved in CH_2Cl_2 (10 ml) and cooled to −78°, then added dropwise to a soln of potassium amide at −78° prepared from ammonia (50 ml), K (65 mg, 1.7 mmol) and ferric nitrate (*ca* 2 mg). After the mixture had been kept for 1 hr at −78° ammonia was removed under reduced pressure, CH_2Cl_2 (25 ml) and water (25 ml) were added, and the organic layer was separated, washed with water, dried ($MgSO_4$) and concentrated. Distillation of the residue gave **14a** as a colourless oil (0.21 g, 73%), b.p. 65° at 0.5 mm Hg (GKR).

The reaction of N-2,2-*trimethyl*-3-*phenylthiopropionamide* (**10a**) *with di-t-butyl peroxide and cupric bromide*

(a) A mixture of the amide (220 mg, 1 mmol), di-t-butyl peroxide (1.0 g, 6.8 mmol), cupric bromide (220 mg, 1 mmol) and naphthalene (10 g) was heated under N_2 at 120–130° for 4 hr. Flash chromatography of the mixture as described above afforded **14a** (39 mg, 18%) and starting **10a** (136 mg, 62%).

(b) A mixture of the amide (220 mg, 1 mmol), di-t-butyl peroxide (1.0 g, 6.8 mmol), and cupric bromide (220 mg, 1 mmol) in refluxing benzene (10 ml) was irradiated under N_2 with a mercury lamp for 3 hr. Work-up as described above afforded **14a** (33 mg, 15%) and **10a** (81 mg, 37%).

No β-lactam (**14a**) was formed when methods (a) or (b) were applied in the absence of the Cu salt.

3-(Phenylthio)propionic acid

Reaction of thiophenol with acrylic acid by the method of Hogeveen and Montanari[23] afforded 3-(phenylthio)propionic acid in 86% yield, m.p. 58–60° (lit.[23] m.p. 59.5–61°).

N-Methyl-3-(phenylthio)propionamide (**10b**)

Treatment of 3-(phenylthio)propionic acid with $SOCl_2$ then $MeNH_2$ as described above gave a solid which crystallised from EtOAc–light petroleum as flakes of *N-methyl-3-(phenylthio)propionamide* **10b** (3.67 g, 82%), m.p. 89–91°. (Found: C, 61.75; H, 6.60; N, 7.42; S, 16.62. $C_{10}H_{13}NOS$ requires: C, 61.51; H, 6.71; N, 7.17; S, 16.42%), δ ($CDCl_3$) 2.38 (2H, t, *J* 7 Hz, CH_2CO), 2.67 (3H, d, *J* 4 Hz, CH_3), 3.12 (2H, t, *J* 7 Hz, CH_2S), 5.9 (1H, b, NH), 7.0–7.4 (5H, m, Ar), ν_{max} 3286, 1641, 1568 cm^{-1}, *m/e* 195 (M^+, 100%), 137 (13%), 123 (38%), 109 (43%), 86 (74%).

The reaction of N-methyl-3-(phenylthio)propionamide (**10b**) *with t-butyl perbenzoate*

Treatment of **10b** with t-butyl perbenzoate in the presence of cuprous bromide as described above for **10a** afforded *3-benzoyloxy-N-methyl-3-(phenylthio)propionamide* (**17**) which crystallised from EtOAc-light petroleum as colourless plates in 72% yield, m.p. 123–127° dec, δ ($CDCl_3$) 2.75 (3H, d, *J* 4 Hz, NCH_3), 2.85 (2H, d, *J* Hz, CH_2), 6.1 (1H, b, NH), 6.6 (1H, t, *J* 7 Hz, CH), 7.1–8.2 (10H, m, Ar), ν_{max} 3300, 1721, 1650, 1552 cm^{-1}, *m/e* 315 (M^+, 1%), 206 (M^+-SC_6H_5, 15%), 194 (M^+-$C_6H_5CO_2$, 2%), 105 (C_6H_5CO, 100%), *m/e* 315–0929 (M^+) (Calc for $C_{17}H_{17}NO_3S$ (M^+) *m/e* 315.0929). The amide (**10b**) (16%) was recovered but no β-lactam or **19** was detected by HPLC.

The reaction of (**10b**) *with di-t-butyl peroxide*

(a) The thermolytic reaction of methyl 3-phenylthiopropionamide with di-t-butyl peroxide as described above, followed by flash chromatography of the product mixture in EtOAc CH_2Cl_2 (20:80) afforded *cis-N-methyl-3-(phenylthio)propenamide* (**19**) which crystallised from EtOAc-light petroleum in 28% yield, m.p. 120–121°. (Found: C, 61.95; H, 5.76; N, 7.12; S, 16.47. $C_{10}H_{11}NOS$ requires: C, 62.14; H, 5.73; N, 7.24; S, 16.58%), δ ($CDCl_3$) 2.84 (3H, d, *J* 4 Hz, NCH_3), 5.85 (1H, d, *J* 10 Hz, CHCO), 6.2 (1H, b, NH), 6.90 (1H, d, *J* 10 Hz, CHS), 7.1–7.6 (5H, m, Ar), ν_{max} 3308, 1636, 1572. 1440 cm^{-1}, *m/e* 193 (M^+, 96%), 163 (M^+-$NHCH_3$, 100%). Continued elution of the column afforded starting material (46%). No β-lactam (**14b**) was detected.

(b) The photolytic reaction of **10b** with di-t-butyl peroxide as described above for **10a** gave similar results to the thermolytic reaction. The propenamide (**19**) was obtained in 21% yield and **10b** (43%) was recovered. No β-lactam (**14b**) was detected.

4-Phenylthioazetidin-2-one

This compound, prepared from vinyl acetate and chlorosulfonylisocyanate *via* 2-oxoazetidin-4-yl acetate in 32% yield by the method of Claub *et al.*[24] had m.p. 72–73° (lit.[24] m.p. 72°).

1-Methyl-4-phenylthioazetidin-2-one (**14b**)

(a) Treatment of 3-benzoyloxy-N-methyl-3-(phenylthio)-propionamide with HBr and subsequently with potassium amide as described above afforded *1-methyl-4-phenylthioazetidin-2-one* (59%), b.p. 60–70° at 0.6 mm Hg (GKR), δ ($CDCl_3$) 2.83 (3H, s, CH_3), 2.5–3.5 (2H, m, CH_2), 4.80 (1H, dd, *J* 2.5 Hz, CH), 7.0–7.5 (5H, m, Ar), ν_{max} 1760 cm^{-1}, *m/e* 193 (M^+, 1%), 136 (M^+-CH_3NCO, 1%), 84 (M^+-SC_6H_5, 100%), *m/e* 193.0556 (M^+) (Calc for $C_{10}H_{11}NOS$ (M^+) *m/e* 193.0561). No **19** was detected.

(b) 4-Phenylthioazetidin-2-one (0.38 g, 2.1 mmol) was dissolved in CH_2Cl_2 (10 ml), cooled to −78°, then added dropwise to a soln of potassium amide at −78° which had been prepared from ammonia (50 ml), K (90 mg, 2.3 mmol) and ferric nitrate (*ca* 2 mg). After the mixture had been kept for 1 hr at −78° a soln of MeI (0.5 g, 3.5 mmol) in CH_2Cl_2 (5 ml) was added dropwise at −78°. After being kept at −78° for a further 1 hr the mixture was worked-up as described above to afford an oil flash chromato-

graphy of which in EtOAc-CH_2Cl_2 (20:80) afforded 1-methyl-4-phenylthioazetidin-2-one (0.26 g, 63%) identical in all respects to the sample obtained as described above. Continued elution of the column afforded starting material (8%).

2-Acetylamino-3-(phenylthio)propionic acid

The reaction of 2-acetylamino-2-propenoic acid with thiophenol by the method of Goodman *et al.*[25] afforded 2-acetylamino-3-(phenylthio)propionic acid (67%), m.p. 151–152° (lit.[25] m.p. 150–151°).

2-Acetylamino-N-methyl-3-(phenylthio)propionamide (**20**)

Treatment of 2-acetylamino-3-(phenylthio)propionic acid with diazomethane in the usual way afforded the methyl ester in 94% yield, δ ($CDCl_3$) 1.85 (3H, s, $COCH_3$), 3.36 (2H, d, *J* 5 Hz, CH_2), 3.52 (3H, s, OCH_3), 4.80 (1H, dt, *J* = 7.5 Hz, CH), 6.45 (1H, b, NH), 7.2–7.4 (5H, m, Ar).

The crude ester was treated with $MeNH_2$ as described above for the acid chlorides. The ppt which formed was dried under vacuum, washed with light petroleum, and crystallised from EtOAc to give needles (87%) of *2-acetylamino-N-methyl-3-(phenylthio)propionamide*, m.p. 160–161°. (Found: C, 56.97; H, 6.49; N, 11.29; S, 12.46. $C_{12}H_{16}N_2O_2S$ requires: C, 57.12; H, 6.39; N, 11.10; S, 12.71%), δ ($CDCl_3$) 1.93 (3H, s, $COCH_3$), 2.70 (3H, d, *J* 5Hz, NCH_3), 3.2 (2H, d, *J* 6 Hz, CH_2), 4.40 (1H, m, CH), 6.3 (2H, b, 2 × NH), 7.1–7.3 (5H, m, Ar), (35% DCl in D_2O) 2.23 (3H, s, $COCH_3$), 2.42 (3H, s, NCH_3), 3.3 (2H, d, *J* 6 Hz, CH_2), 4.6 (1H, t, *J* 6 Hz, CH), 7.1–7.3 (5H, m, Ar), *m/e* 252 (M^+, 17%), 193 (100%), 163 (26%), 135 (30%), 110 (35%), 109 (19%).

Reactions of 2-acetylamino-N-methyl-3-(phenylthio)propionamide (**20**)

(a) Treatment of **20** (100 mg, 0.4 mmol) with t-butyl perbenzoate (100 mg, 0.52 mmol) and cuprous bromide (10 mg) in refluxing benzene for 6 hr gave a complex product mixture from which no pure compound could be isolated. However, when the reaction was repeated and worked up after 20 min by flash chromatography in EtOAc-CH_2Cl_2 (20:80), it afforded a single product as an oil (4%), tentatively assigned the structure 2-acetylamino-N-methyl-propenamide, δ ($CDCl_3$) 2.10 (3H, s, CH_3CO), 2.90 (3H, d, *J* 4 Hz, NCH_3), 5.18 and 6.36 (2H, m, m, CH_2), 7.6 (2H, m, 2 × NH). Attempts to obtain an analytically pure sample or to prepare the authentic compound were unsuccessful. The starting amide (83%) was also isolated.

(b) Treatment of **20** (100 mg, 0.4 mmol) with di-t-butyl peroxide (400 mg, 2.75 mmol) and cupric bromide, *either* in naphthalene (50 g) at 120–130°, *or* in benzene (100 ml) under UV irradiation gave an intractable complex mixture of products in each case.

3-Carbomethoxy-5-oxoperhydro-1,4-thiazepine (**23a**)

The reaction of methyl acrylate and L-cysteine hydrochloride hydrate[26] gave **23a** (42%) which crystallized from ether as needles, m.p. 109–110° (lit.[26] m.p. 91–92°). Spectra were consistent with those reported.[26]

3-Carbomethoxy-2,2-dimethyl-5-oxoperhydro-1,4-thiazepine (**23b**)

3-Carboxy-2,2-dimethyl-5-oxoperhydro-1,4-thiazepine (27%), prepared from methyl acrylate and D-penicillamine,[27] was treated with diazomethane in the usual way to give **23b** (92%) which crystallised from hexane as needles, m.p. 107–110° (lit.[28] 103.5–105.5°). Spectra were consistent with those reported.[28]

Methyl penicillinate

Penicillanic acid (51%), obtained from 6-aminopenicillanic acid *via* the bromide,[29] was treated with diazomethane in the usual way to give methyl penicillinate (82%), which crystallised from light petroleum as colourless plates, m.p. 48–50° (lit.[30] m.p. 52–53°).

Reactions of 3-carbomethoxy-5-oxoperhydro-1,4-thiazepine (**23a**)

(a) The thiazepine **23a** (500 mg, 2.7 mmol), t-butyl perbenzoate (1.0 g, 51 mmol) and cuprous bromide (100 mg) were heated in benzene (1 l.) under reflux for 6 hr. Flash chromatography of the product mixture in ether afforded 3-carbomethoxy-5-oxo-4,5,6,7-tetrahydro-1,4-thiazepine (54 mg, 11%), m.p. 88–89° (lit.[26] m.p. 88–89°), 3-carbomethoxy-5-oxo-2,3,4,5-tetrahydro-1,4-thiazepine (70 mg, 13%), m.p. 125–126° (lit.[26] m.p. 131–132°), and starting material (40%). No β-lactam or benzoyloxylated product could be detected.

(b) Treatment of **23a** (50 mg, 0.27 mmol) with di-t-butyl peroxide (1.5 g, 10.2 mmol) and cupric bromide (*ca* 10 mg) *either* in naphthalene (50 g) at 120–130°, *or* in benzene (100 ml) with UV irradiation gave a complex intractable mixture in each case.

Reactions of 3-carbomethoxy-2,2-dimethyl-5-oxoperhydro-1,4-thiazepine (**23b**)

Treatment of **23b** (50 mg, 0.23 mmol) with t-butyl perbenzoate or di-t-butyl peroxide as described for **23a** gave only intractable mixtures of products. The expected β-lactam (methyl penicillinate) could not be detected.

The reaction of dimethyl disulfide with t-butyl perbenzoate

A soln of Me_2S_2 (47.1 g, 0.5 mmol) and t-butyl perbenzoate (97.1 g, 0.5 mol) in benzene (500 ml) under N_2 was heated under reflux for 60 hr, then cooled and concentrated under reduced pressure. Flash chromatography of the residue in light petroleum-CH_2Cl_2 (1:1), afforded benzoyloxymethyl methyl disulfide as a pale yellow oil (1.6 g, 1.5%), δ ($CDCl_3$) 2.46 (3H, s, CH_3), 5.50 (2H, s, CH_2), 7.2–8.3 (5H, m, Ar), ν_{max} 1728 cm^{-1}, *m/e* 214 (M^+, 7%), 184 (M^+-OCH_2, 100%), 135 (M^+-$SSCH_3$, 45%), 122 ($C_6H_5CO_2H$, 82%), 105 (M^+-OCH_2SSCH_3, 51%); *m/e* 184.0014 (M^+-OCH_2) (Calc for $C_8H_8OS_2$ (M^+-OCH_2) *m/e* 184.0017). The product decomposed upon attempted distillation. When this reaction was repeated with added cuprous bromide the result was the same.

The reaction of benzoyloxymethyl methyl disulfide with hydrogen bromide

Flash chromatoggraphy (CH_2Cl_2) of the product obtained by treatment of benzoyloxymethyl methyl disulfide in CH_2Cl_2 with HBr for 10 hr as described above afforded an oil which was distilled to give bromomethyl methyl sulfide as a colourless oil (0.44 g, 72%), b.p. 30–35° at 18 mg Hg (GKR) (lit.[31] b.p. 29–32° at 13 mm Hg), δ ($CDCl_3$) 4.60 (2H, s, CH_2), 2.55 (3H, s, CH_3). The ^1H NMR spectrum of the crude mixture contained resonances assigned to this sulfide and benzoic acid, and singlets at δ 5.23 and 2.36 which integrated in the ratio 2:3 and were assigned to bromomethyl methyl disulfide. Integration of the ^1H NMR spectrum indicated a ratio of sulfide to disulfide of about 1:1 which, on taking into account the high yield of sulfide obtained from the chromatography column, indicates the rearrangement of the disulfide to the sulfide on the column. Sampling of the reaction mixture during the course of the reaction indicated that the disulfide was intermediate in the conversion of the benzoate to the sulfide. Distillation of the crude mixture afforded only the sulfide.

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