A New Rearrangement Reaction of Penicillin G Sulphoxide

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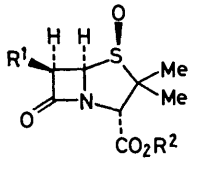
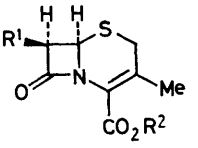
Penicillin G sulphoxide on reaction with trifluoroacetic anhydride gave, in high yield, a novel tricyclic spiro-derivative. Reaction with toluene-α-thiol gave *S*-benzyl thioformate and (2*S*,5*S*)-2-benzylthiocarbonyl-6,6-dimethyl-3-phenylacetyl-5-trifluoroacetamido-1,3-thiazin-4-one.

THE conversion of penicillin sulphoxide derivatives (1) into deacetoxycephalosporin (2) analogues by reaction with acetic anhydride is well known.[1] Minor non-β-lactam products (3)—(5) are also formed in the reaction. During recent work on the preparation of novel 2-acetyldeacetoxycephalosporins[2] and modification of the penicillin side chain[3] the reaction of penicillins and cephalosporins with trifluoroacetic anhydride was examined. The acid-labile[1] β-lactam functions of both penicillin G (*S*-deoxy-1a)[3] and its β-sulphoxide (1a) were cleaved under the reaction conditions. The β-sulphoxide (1a) gave a novel rearrangement product. Rapid chromatography on Merck Kieselgel 60 provided a crystalline product (A) in high yield. The product was not stable to preparative layer or column chromatography on Kieselgel GF_{254} or H respectively. Thus repeated crystallisation was required to remove the impurity, a minor intense lemon-yellow pigment.



(1)



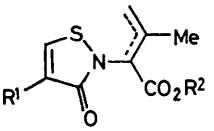
(2)

a; R^1 = $PhCH_2CONH$, R^2 = H

b; R^1 = NH_2, R^2 = H, zwitterion,1-deoxy

c; R^1 = AcNH, R^2 = H

d; R^1 = $Ph_2CHCONH$, R^2 = H



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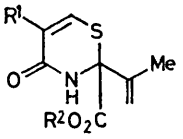

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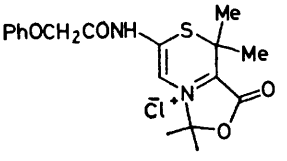
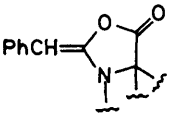
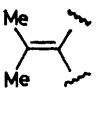


(5)

Analysis and the high-resolution mass spectrum showed the compound (A) to be $C_{18}H_{15}F_3N_2O_5S$. It did not contain the phenylacetamido-methylene (n.m.r.). Both the i.r. (1 825 cm^{-1}) and u.v. [λ 284 nm (ε 26 000)] spectra were consistent with the partial structure (6). Consistent with this, ozonolysis gave benzaldehyde



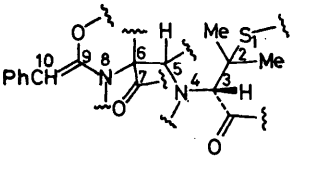
(6)



(7)

(96%) isolated as its 2,4-dinitrophenylhydrazone. Acetone was not formed in the ozonolysis, thus the isopropylidene function (7) was absent. The absence of olefin (7) was also consistent with the high-field methyl resonances in the ^1H (τ 8.34, 8.39, 8.43, and 8.46) and ^{13}C (δ 31—24) n.m.r. spectra, and the C-2 resonance at δ 52.2 and 51.7. I.r. absorption at 1 725 but not at 1 780 cm^{-1} suggested a trifluoroacetamido-function rather than a trifluoroacetate.

The penicillin sulphoxide nucleus (1) usually fragments between C(5)–S(1) and N(4)–C(7) † on reaction with electrophiles, thus the framework (8) is probably present in (A), and a combination of the partial structures (6) and (8) suggested structure (9). Adduct (A) did not



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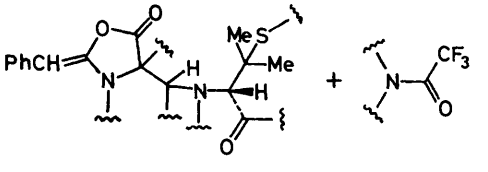


(9)

react with triphenylphosphine or trimethyl phosphite (room temperature), or norbornadiene (under reflux), and thus did not contain a sulphenate or sulphoxide function capable of thermally generating a sulphenic acid. (A) did not contain a carboxy-function since it was non-polar (t.l.c.), and addition of diethylamine at 0 °C and evaporation gave unchanged (A). The position

† For convenience, the penicillin numbering system is retained for compound (A) and its derivatives although systematic numbering is used in the abstract.

of the methyl resonances in both the ^{13}C and ^{1}H n.m.r. spectra were also consistent with the S(1)–C(2) bond being intact and the absence of a sulphoxide function (since the methyl resonances did not differ appreciably in chemical shift).

Although homogeneous on t.l.c., duplication of n.m.r. signals and a diffuse m.p. suggested that (A) was a mixture of two isomers. Separation by repeated crystallisation failed (n.m.r. and m.p.) and thus an *X*-ray crystallographic study was not possible. Initially the origin of the isomers was considered to result from geometrical isomerism in the styrene unit (6). Thus attempts were made to prepare an analogue of (A) equivalently disubstituted at C(10).

Reaction of 6-aminopenicillanic acid (6-APA) (1b) with acetic anhydride–triethylamine and subsequently with sodium metaperiodate gave the acetamido-sulphoxide (1c). Trifluoroacetylation of (1c) resulted in β-lactam cleavage giving a complex mixture lacking an analogue of (A) (n.m.r., i.r.). The diphenylacetamido-sulphoxide (1d) was also prepared from 6-APA (1b) by reaction with diphenylacetyl chloride and sodium metaperiodate in sequence. Reaction with $(CF_3CO)_2O$ gave a crystalline product (accompanied by a minor deep red pigment). Both analysis and the high-resolution mass spectrum suggested the formula $C_{24}H_{19}F_3N_2O_5S$, consistent with the phenyl analogue of (A). Both the i.r. (1 825 cm^{-1}) and u.v. [λ 292 nm (ε 17 500)] spectra supported this correlation. The n.m.r. spectrum was similar to that of (A) with two exceptions: the single-proton resonance in (A) at τ 3.36 was absent, and integration showed five additional aromatic protons to be present. Again, however, both the diffuse melting point and the n.m.r. spectrum showed the compound to consist of two isomers inseparable by fractional crystallisation. Clearly the isomerism did not derive from the styrene unit (6).

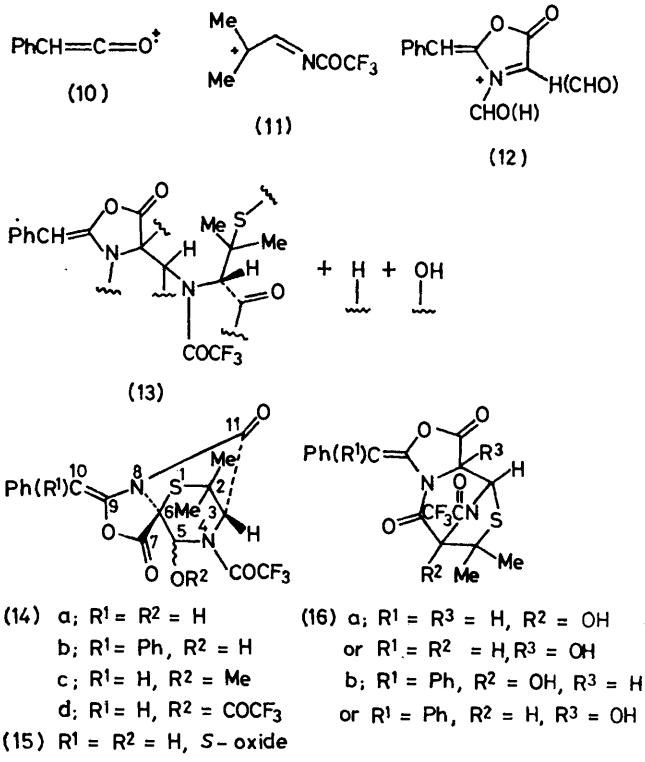
Comparison of the high-resolution mass spectra of the unknown (A) and its phenyl analogue permitted assignments of fragment compositions (see Table). Plausible

Mass-spectral fragmentation of adducts (14a) and (14b)

(14a) a.m.u.	(14b) a.m.u.
399 $[M - CHO]^+$	476 $[M - CO]^+$
371.0674 $[M - CO - CHO]^+$	Weak ion at 447 $[M - CHO - CO]^+$
206.0281 $[C_{10}H_8NSO_2]^+$	282 $[C_{16}H_{12}NSO_2]^+$ (206 absent)
202.0518 * $[C_{11}H_8NO_3]^+$	278 $[C_{17}H_{12}NO_3]^+$ (202 absent)
166.0493 $[C_6H_7NOF_3]$	166 $[C_6H_7NOF_3]^+$ (242 absent)
118 * $[C_8H_6O]^+$? Phenylketen$^{+\cdot}$?	193, 195 (118 absent)

* The ions at *m/e* 202 and 118 were also present in the per-acid oxidation product of (A); the latter was also present in the *O*-methyl derivative of (A).

structures for the fragments at *m/e* 118, 166, and 202 were ions (10), (11), and (12). Ion (11) suggested the trifluoroacetyl function in adduct (A) was bonded to N(4), suggesting the partial structure (13). Plausibly, (A) and phenyl-(A) were the amide derivatives (14a) and (14b) respectively. The alternative structures (16a and b) were discounted by the absence (excluding the aromatic protons) of any significant proton–proton



(14) a; $R^1 = R^2 = H$
b; R^1 = Ph, $R^2 = H$
c; $R^1 = H$, R^2 = Me
d; $R^1 = H$, $R^2 = COCF_3$
(15) $R^1 = R^2 = H$, *S*-oxide

(16) a; $R^1 = R^3 = H$, R^2 = OH or $R^1 = R^2 = H$, R^3 = OH
b; R^1 = Ph, R^2 = OH, $R^3 = H$ or R^1 = Ph, $R^2 = H$, R^3 = OH

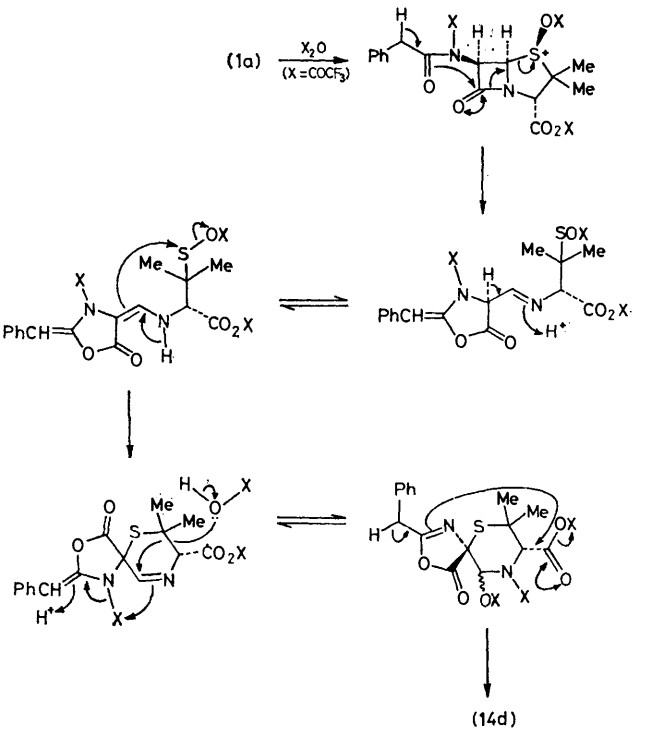
spin coupling and subsequent reactions (see below). The stereochemistry of the optically active adducts (14a) and (14b) followed from the chirality at C(3). The trifluoroacetylamine is not unreasonable in that it is held together by the cage structure (Dreiding models) and accounts for the existence of the two isomers. Hydrogen bonding between the hydroxy and the trifluoroacetyl oxygen may also contribute to the stability of (A) (14a).

Amine (A) (14a) can be considered to arise by trifluoroacetylation of the C(11) carboxy, N(8) amide, and S(1) sulphoxide in sequence [4] followed by C(5)–S(1) cleavage.[2] Subsequent β-lactam cleavage and recyclisation is summarised (Scheme 1). The exact sequence of steps is, however, not clear. Presumably the *O*-trifluoroacetate (14d) is rapidly hydrolysed on the aqueous strongly acidic work-up.

The trifluoroacetylamine (14a) gave complex mixtures on reaction with lithium iodide, aqueous sodium periodate, aniline, benzylamine, diethylamine (prolonged reaction), or lithium aluminium hydride in THF. Attempted hydrolysis with an excess of sodium hydrogencarbonate or potassium carbonate (1.05 equiv.) in methanol or on B.D.H. MFC silica also gave intractable mixtures. The derivative (14a) was inert to norbornadiene in THF (1 : 1) under reflux for 9 h, acetic anhydride, trimethyl phosphite, triphenylphosphine, pyridine, or toluene-α-thiol in $(CD_3)_2CO$.

Reaction with diazomethane or methyl fluoro-

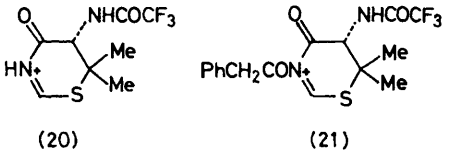
sulphonate in the presence of ethyldi-isopropylamine gave a monomethyl derivative (14c) as a foam. The formula $C_{19}H_{17}F_3N_2O_5S$ was in full agreement with the



SCHEME 1

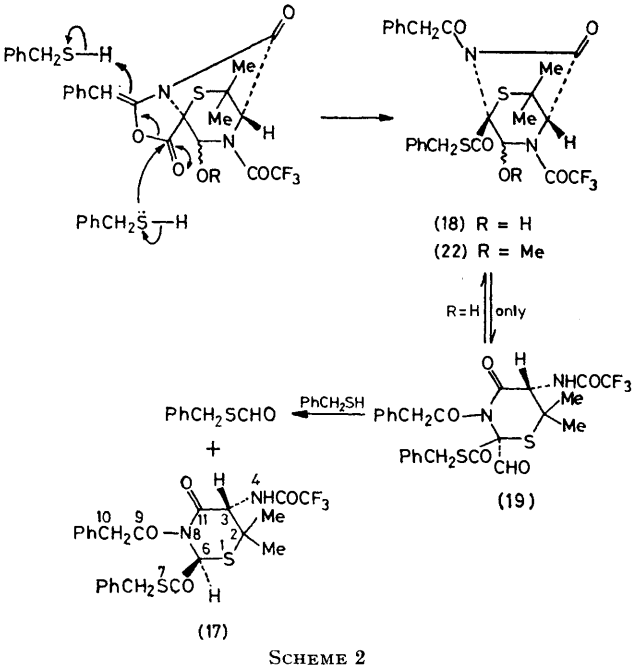
analysis and high-resolution mass measurement. The i.r. (1 825 cm^{-1}) and u.v. [λ 284 nm (ε 24 000)] spectra indicated that the adduct skeleton (14) was intact. Again the n.m.r. spectrum showed two isomers to be present. Both compounds were clearly *O*-methyl derivatives (τ 6.32, 6.49). By analogy with adduct (A) (14a) these were assigned as the epimeric ethers (14c).

Reaction of adduct (A) (14a) with toluene-α-thiol in the presence of pyridine gave a crystalline product (B). The analysis and high-resolution mass measurement were in excellent agreement with the formula $C_{24}H_{23}F_3N_2O_4S_2$. Thus the reaction involved addition of toluene-α-thiol and loss of carbon monoxide. In addition several minor unidentified by-products were formed, one of which showed a strong carbonyl absorption at 1 780 cm^{-1} but since it was an inhomogeneous oil (n.m.r.) structural assignment was impossible. The crystalline product did not contain the benzylideneisoxazolidinone ring (6) (u.v., i.r.) and the n.m.r. spectrum showed two aromatic methylene groups both as AB quartets (τ 5.6 and 5.73). The n.m.r. spectrum and sharp melting point confirmed the derivative to be a single compound. The trifluoroacetamido-N–H (τ 1.16) was coupled to a single proton, presumably H(3) (τ 4.9). Most reasonably (B) was the more stable *trans*-diacylamine (17) formed *via* (18) and (19) (Scheme 2). Consistent with this, *S*-benzyl thioformate (identical with an authentic specimen [5]) was also formed. Fragmentation of (B) (17) in the mass spectrum included ions at *m/e* 255 and 373, assigned structures (20) and (21) respectively.



The methyl ether (14c) also reacted with toluene-α-thiol and pyridine to give a crystalline solid in high yield. Analysis ($C_{26}H_{25}F_3N_2O_5S_2$) showed the addition of toluene-α-thiol but no deformylation. By analogy with (A) (14a), initial fragmentation of the benzylideneisoxazolidinone ring (6) by attack at C(7) would be expected (Scheme 2). The initial product (22) would not be able to ring-open and thus deformylate. All spectral data supported assignment of the product as the amine ether (22) (see Experimental section). As expected, the product consisted of two epimers (n.m.r.), although it was homogeneous by t.l.c.

Adduct (A) (14a) reacted with peracetic acid to give a more polar unstable derivative. Since the compound was an impure oil which decomposed on attempted chromatography microanalysis was not possible. How-



SCHEME 2

ever, both the i.r. (1 825 cm^{-1}) and u.v. [λ 286 nm (ε 21 000)] spectra suggested an intact styrene unit (6). The mass spectrum showed the product to be a monooxygenated derivative, plausibly a sulphoxide (15).

EXPERIMENTAL

Melting points were recorded on a Kofler hot stage. P.l.c. was carried out on Merck GF_{254} Kieselgel. Column chromatography was carried out on Merck Kieselgel 60 or H. The following purified solvents were used: dichloro-

methane (freshly distilled from P_4O_{10}), triethylamine or di-isopropylethylamine (freshly distilled from sodium), and pyridine (freshly distilled from a 4A molecular sieve). Petroleum and light petroleum refer respectively to the redistilled fractions with b.p. 60—80 and 40—60 °C. Organic extracts were dried over anhydrous sodium sulphate.

Preparation of the Rearrangement Product (14a).—Penicillin G sulphoxide (1a) (3.5 g), trifluoroacetic anhydride (5 ml), and dry dichloromethane (50 ml) were stirred at room temperature for 20 h. The solution was washed with water (100 ml), dried, evaporated, and chromatographed on Merck Kieselgel 60 (40 g) (eluant CH_2Cl_2) to give the *rearrangement product* (A) (14a) [3.3 g, 77%, ≥95% pure (n.m.r.)] as a lemon yellow solid. The product in CH_2Cl_2 was boiled with charcoal, filtered through Celite, and evaporated to dryness. The solid (2.93 g) was extracted with diethyl ether (10 ml) and diethyl ether–light petroleum (1 : 2) (3 × 10 ml) and the residue recrystallised, after treatment with charcoal, from dichloromethane–light petroleum to give (A) (14a) (1.18 g) as rosettes of white needles, m.p. 200—209 °C (bulk 206—209 °C), $[\alpha]_D^{20}$ −118° (*c* 0.774, THF), $\nu_{max.}$ (Nujol) 3 520s, 1 825s, 1 710s, 1 690m, 1 665m, 1 413m, 1 330m, 1 315w, 1 270m, 1 260w, 1 235m, 1 215m, 1 188m, 1 150m, 1 130m, 1 080m, 1 035m, 1 020w, 1 010w, 930w, 918w, 850w, 835m, 785w, 760m, 725m, 698m, and 660w cm^{-1}; $\nu_{max.}$($CHCl_3$) 3 500—3 300m,br, 1 825s, 1 725s, 1 690s, 1 600w, 1 450m, 1 390s, 1 150s, 1 130s, 1 010s, and 915w cm^{-1}; $\lambda_{max.}$(THF) 284 nm (ε 26 000); τ[$(CD_3)_2CO$] 2.12—2.22 (1 H, m, exchangeable with D_2O, OH), 2.46, 2.63, 2.73 (5 H, m, aryl-H), 3.355, 3.364 (1 H, 2 s, 10-H), 3.9 (1 H, br s, 3-H), 4.7 (*ca.* 2/3 H, s, 5-H), 5.21 (*ca.* 1/3 H, s, 5-H), 8.34, 8.39, 8.43, and 8.46 (6 H, 4 s, ratio *ca.* 1 : 1 : 2 : 2, 2-Me_2), ^{13}C [$(CD_3)_2CO$] δ 160.2 (s), 139.1 (s), 133.6 (s), 132.5 (s), 128.95 (d, *J* 105 Hz), 128.88 (d, *J* 108 Hz), 128.5 (d, *J* 103 Hz), 128.4 (d, *J* 106 Hz), 127.5 (d, *J* 105 Hz), 127.3 (d, *J* 105 Hz), 122.0 (s), 121.6 (s), 110.6 (s), 93.4 (d, *J* 101 Hz), 81.8 (2 d, *J* 104 Hz), 66.5 (d, *J* 84 Hz), 64.4 (d, *J* 88 Hz), 52.2 (s), 51.7 (s), and 31—24 (methyls) (the low intensity of some signals, signal overlap, and overlap of the methyl peaks with those from the solvent prevented full spectral assignment); *m/e* 428 (M^+), 399, 371.067 4 ($C_{16}H_{14}F_3N_2O_3S$ requires 371.067 7 [(M − CO − CHO)$^+$], 282, 258, 240.055 3, 206.028 1 ($C_{10}H_8NO_2S$ requires 206.027 6), 202.051 8 ($C_{11}H_8NO_3$ requires 202.050 4), 167, 166.049 3 [$C_8H_8NO_3$ requires 166.050 4, or $C_6H_7F_3NO$ requires 166.047 7; since this fragment is present in the mass spectrum of (14b), the latter is correct], and 118 (Found: C, 50.65; H, 3.55; N, 6.55; S, 7.8%; *M* 428.065 1. $C_{18}H_{15}F_3N_2O_5S$ requires C, 50.45; H, 3.55; N, 6.55; S, 7.5%; *M* 428.065 4).

Ozonolysis of Adduct (A) (14a).—Ozone was bubbled through a solution of adduct (14a) (135 mg) in CH_2Cl_2 (30 ml) at −70 ± 4 °C. When permanently blue the solution was purged with dry nitrogen at −70 °C and triphenylphosphine (77 mg) added. After 100 min at room temperature 2,4-dinitrophenylhydrazine (160 mg) was added and the mixture stirred at room temperature for 25 min. Chromatography on Kieselgel 60 (10 g) (eluant CH_2Cl_2) gave benzaldehyde 2,4-dinitrophenylhydrazone (87 mg, 96%), m.p. 240—241 °C (from DMF–ethanol) (lit.,[6] 237 °C). Acetone 2,4-dinitrophenylhydrazone was not formed. A blank reaction with the subsequent addition of acetone (10 μl) gave acetone 2,4-dinitrophenylhydrazone (23 mg, 71%), m.p. 127—128 °C (lit.,[6] 128 °C). Omission of 2,4-dinitrophenylhydrazine gave an oil containing benzaldehyde and several unstable polar sulphur-containing species (t.l.c.).

Preparation of (1S,3S,5R,6R)-6-*Acetamido*-2,2-*dimethylpenam*-3-*carboxylic Acid* 1-*Oxide* (1c).—Triethylamine (0.633 ml, 1.1 equiv.) and acetic anhydride (0.510 ml, 1.3 equiv.) were added in sequence to a slurry of 6-aminopenicillanic acid (1b) (897 mg) in dry THF (40 ml). The mixture was stirred at room temperature overnight and unchanged (1b) (91 mg) filtered off. The mother liquor on evaporation was combined with additional acetylated product from (1b) (216 mg). The oil was dissolved in water (35 ml) with $NaHCO_3$ (389 mg). Phosphate buffer (9.5 ml; 0.2M, pH 6.8) and sodium periodate (1.16 g) in water (35 ml) were added in sequence. After 3 h the solution was cooled to 0 °C and 20% aqueous orthophosphoric acid added to pH 2.0. The solution was saturated with sodium sulphate and extracted with ethyl acetate (2 × 100 ml). The organic phase was washed with water (2 × 5 ml), dried, evaporated to dryness, and the residue triturated with acetone and subsequently carbon tetrachloride–light petroleum to give the *sulphoxide* (1c) (342 mg, 24%) as a white crystalline solid. Recrystallisation from acetone–light petroleum gave material with m.p. 189—192 °C (decomp.), $[\alpha]_D^{23}$ +297° (*c* 0.156, EtOH), $\nu_{max.}$(Nujol) 3 400m, 2 600m,br, 1 800s, 1 730s, 1 695s, 1 650s, and 1 540m cm^{-1}, τ[$(CD_3)_2SO$)] 2.25 (1 H, d, *J* 9 Hz, NH), 4.2 (1 H, dd, *J* 9 and 4 Hz, 6-H), 4.6 (1 H, d, *J* 4 Hz, 5-H), 5.62 (1 H, s, 3-H), 8.05 (3 H, s, NAc), 8.4 (3 H, s, 2β-Me), and 8.8 (3 H, s, 2α-Me) (Found: C, 44.05; H, 5.2; N, 10.05. $C_{10}H_{14}N_2O_5S$ requires C, 43.75; H, 5.15; N, 10.2%).

Reaction of the Sulphoxide (1c) *and Trifluoroacetic Anhydride.*—Reaction of (1c) (60 mg) and trifluoroacetic anhydride (0.2 ml) in dichloromethane (2 ml) for 14 h at room temperature gave an evil smelling polar oil. The n.m.r. spectrum indicated a complex mixture, which lacked the signals attributable to the acetyl analogue of (A).

Preparation of (1S,3S,5R,6R)-2,2-*Dimethyl*-6-(*diphenylacetamido*)*penam*-3-*carboxylic Acid* 1-*Oxide* (1d).—A solution of diphenylacetyl chloride (0.62 g, 1.32 equiv.) in dry acetone (6 ml) was added dropwise during 8 min to a vigorously stirred solution of (1b) (532 mg) and $NaHCO_3$ (0.47 g, 2.8 equiv.) in water (14 ml) and acetone (12 ml). After 35 min, acetone was removed under reduced pressure and the residue dissolved in phosphate buffer (5 ml; 0.2M, pH 6.8). Sodium periodate (0.50 g) in water (15 ml) was added and the mixture stirred at room temperature for 3 h. The usual work-up gave a solid that was washed with diethyl ether (2 × 10 ml) (to remove Ph_2CHCO_2H) and dried to give the *diphenylacetamide* (1d) as a crystalline solid (0.66 g, 77%); $\nu_{max.}$(Nujol) 3 480m, 3 200—2 400m, 1 790s, 1 745s, 1 642s, 1 510s, 1 292m, 1 218m, 1 015m, 750m, 730m, 700m, and 695m cm^{-1}; τ[$(CD_3)_2SO$] 2.02 (1 H, d, *J* 9 Hz, NH), 2.74 (10 H, m, aryl-H), 4.28 (1 H, dd, *J* 9 and 4.5 Hz, 6-H), 4.67 (1 H, d, *J* 4.5 Hz, 5-H), 4.75 (1 H, s, Ph_2CH), 5.72 (1 H, s, 3α-H), 8.48 (3 H, s, 2β-Me), and 8.87 (3 H, s, 2α-Me). Recrystallisation from aqueous methanol gave material with m.p. 203—205.5 °C (decomp.), $[\alpha]_D^{21}$ +215° (*c* 0.332, DMSO), *m/e* 332, 252, 167, 165, and 114 (Found: C, 61.7; H, 5.2; N, 6.45%. $C_{22}H_{22}N_2O_5S$ requires C, 61.95; H, 5.2; N, 6.55%).

Reaction of Diphenylacetamide (1d) *with Trifluoroacetic Anhydride.*—Reaction of diphenylacetamide (1d) (968 mg) and trifluoroacetic anhydride (4 ml) in dry dichloromethane

(8 ml) for 23.5 h at room temperature and work-up gave on chromatography on Kieselgel 60 [eluant CH_2Cl_2–petroleum (1 : 1—1 : 0) adduct (14b) as a red solid (429 mg, 37%). Boiling with charcoal, filtration, and recrystallisation gave (14b) as rosettes of white needles (228 mg), m.p. 220—226 °C (decomp.), $[\alpha]_D^{20}$ +113° (*c* 0.435, THF); $\nu_{max.}$(CCl_4) 3 600—3 100m,br, 1 825s, 1 740—1 700s,br, 1 660m, 1 450m, 1 350m, 1 230s,br, 1 160s, 1 135s, and 698s cm^{-1}; $\lambda_{max.}$(THF) 230 (ε 17 500) and 292 nm (17 500); τ[$(CD_3)CO$] 2.76 (11 H, aryl-H + OH), 4.0 (1 H, s, 3-H), 5.03, 5.55 (1 H, 2 s, ratio *ca.* 2 : 1, 5-H), and 8.4, 8.55 (6 H, 2 s, ratio *ca.* 2 : 1, 2-Me_2); *m/e* 504 (M^+), 476, 460, 447, 432, 319, 278, 195, 193, 167, 166, and 165 (Found: C, 57.0; H, 3.85; N, 5.6%; *M* 504.097 6. $C_{24}H_{19}F_3N_2O_5S$ requires C, 57.1; H, 3.8; N, 5.55%; *M* 504.096 7).

Reaction of (14a) *and Diazomethane.*—Excess of diazomethane [from *N*-methyl-*N*-nitrosourea (2 g)] in diethyl ether (2 ml) was added to (14a) (502 mg) in dry THF (4 ml) at 0 °C. After 3.5 h acetic acid (5 drops) was added and the mixture evaporated to dryness: chromatography [Kieselgel H (12 g), benzene–light petroleum (4 : 1)] gave the *methyl ether* (14c) (157 mg, 30%) as a foam and (14c) (41 mg) contaminated by a more polar impurity; $[\alpha]_D^{20}$ −118° (*c* 0.897, THF); $\nu_{max.}$ ($CHCl_3$) 1 825s, 1 720s, 1 690m, 1 600w, 1 385s, 1 150s, 1 130s, 1 085m, and 1 015w cm^{-1}; $\lambda_{max.}$ (THF) 284 nm (ε 24 000); τ($CDCl_3$) 2.5, 2.66, 2.77 (5 H, m, aryl-H), 3.34, 3.38 (1 H, 2 s, ratio *ca.* 1 : 2, 10-H), 4.36 (1 H, s, 3-H), 4.75, 5.48 (1 H, 2 s, ratio *ca.* 1 : 2, 5-H), 6.32, 6.49 (3 H, 2 s, ratio *ca.* 2 : 1, OMe), 8.47, and 8.52 (6 H, 2 s, 2-Me_2); *m/e* 442 (M^+), 415, 395, 383, 345, 324, 317, 259, 216, 188, 160, 158, and 118 (Found: C, 51.7; H, 3.95; N, 6.15%; *M* 442.081 6. $C_{19}H_{17}F_3N_2O_5S$ requires C, 51.55; H, 3.9; N, 6.35%; *M* 442.081 0).

Reaction of (14a) *and Methyl Fluorosulphonate.*—Methyl fluorosulphonate (0.162 ml, 2 equiv.) and dry di-isopropylethylamine (0.261 ml, 1.5 equiv.) were added in sequence to a slurry of (14a) (428 mg) in dry dichloromethane (4 ml) at −10 °C. The solid rapidly dissolved and after 23 min di-isopropylethylamine (0.03 ml) was added. After 12 min, the solution was diluted with dichloromethane (20 ml), washed with water (2 × 20 ml), dried, and evaporated to dryness. Chromatography [Kieselgel H (15 g); toluene–light petroleum (7 : 3—5 : 1)] gave the methyl ether (14c) (248 mg, 56%) identical (t.l.c., n.m.r., and reaction with toluene-α-thiol) with the diazomethane product.

Reaction of Adduct (A) (14a) *with Toluene-α-thiol.*—Toluene-α-thiol (0.137 ml, 1.1 equiv.) and dry pyridine (0.096 ml) were added in sequence to (A) (14a) (444 mg) in dry acetone (2.4 ml) under N_2. After 18 h, dry toluene (5 ml) was added and the mixture evaporated to leave a pink crystalline solid which was recrystallised from diethyl ether to give *thioester* (B) (17) as white prisms (115 mg, 21%), m.p. 195—197 °C, $[\alpha]_D^{20}$ −35° (*c* 0.295, THF); $\nu_{max.}$ ($CHCl_3$) 3 380m, 2 920w, 1 735(sh), 1 720s, 1 678s, 1 600w, 1 490w, 1 450w, 1 370w, 1 340m, 1 300w, 1 158s, and 1 120m cm^{-1}; $\lambda_{max.}$ [EtOH–Et_2O (1 : 1.5)] 217.5 (ε 14 700) and 237sh nm (7 500); τ[$(CD_3)_2CO$] 1.16br (1 H, d, *J* 8.5 Hz, exchangeable with D_2O, N–H), 2.72 (10 H, m, aryl-H), 3.4 (1 H, s, 6-H), 4.9 (1 H, d, *J* 8.5 Hz, s with D_2O, 3-H), 5.6 (2 H, AB q, *J* 16.5 Hz, aryl-CH_2), 5.73 (2 H, AB q, *J* 13.5 Hz, aryl-CH_2), 8.52 (3 H, s, 2-Me), and 8.73 (3 H, s, 2-Me); *m/e* 524 (M^+), 496, 439, 406, 400, 383, 373, 255, 118, and 91 (Found: C, 55.0; H, 4.35; N, 5.3; S, 11.9%; *M* 524.103 8. $C_{24}H_{23}F_3N_2O_4S_2$ requires C, 54.95; H, 4.4; N, 5.35; S, 12.25%; *M* 524.105 2). Repeated p.l.c. [silica; EtOAc–petroleum (15 : 85—17 : 83)] of the mother liquor gave (in order of increasing polarity) an oily product derived from toluene-α-thiol only (37 mg), additional thioester (B) (17) (17 mg, total 24%), and three additional products (I), (II), and (III). (I) (164 mg) was an oil, $\nu_{max.}$ ($CHCl_3$) 3 540w, 3 370m, 1 780s, 1 735s, 1 685s, 1 620w, 1 600w, 1 492w, 1 450m,br, 1 372m, 1 310s, 1 160s, 1 015w, and 940w cm^{-1}; τ($CDCl_3$) 2.13, 2.5, 2.65, 2.68, 2.85, 3.92, 4.83, 4.95, 5.75, 5.94, 6.6, 8.48, and 8.72; *m/e* 474, 449, 410 (all weak ions), 383.068 4, 351, 314, and 190: (II) was a complex mixture of products (37 mg): and (III) (114 mg) was an oil, $\nu_{max.}$ ($CHCl_3$) 3 460m, 1 785m, 1 735s, 1 685, 1 300m, and 1 160m, τ($CDCl_3$) 2.68, 4.95, 5.0, 5.8, 6.05, 7.4, 7.88, 8.48, 8.52, 8.6, 8.7, and 8.8; *m/e* 449, 410, 390, 383, 351, 255, 194, 190, 166, and 91. Neither (I) nor (II) could be obtained crystalline or pure (multiple development t.l.c.). A repeat reaction with adduct (14a) (1.576 g) gave on evaporation with toluene an oily solid that was extracted with light petroleum (3 × 10 ml). The solvent was evaporated off and chromatography [Kieselgel H (10 g); dichloromethane–light petroleum (1 : 1)] gave *S*-benzyl thioformate (63 mg, 11%) identical (i.r., n.m.r., t.l.c.) with an authentic sample.[5] Reaction of adduct (14a) with toluene-α-thiol (2 equiv.) and pyridine (1 equiv.) gave on crystallisation the acylamide (17) (21%), and on light petroleum extraction *S*-benzyl thioformate [14% (n.m.r.)].

Reaction of the Methyl Ether (14c) *with Toluene-α-thiol.*—Thiol-α-thiol (0.074 ml, 1.1 equiv.) and dry pyridine (0.045 5 ml, 1 equiv.) were added in sequence to the methyl ether (14c) (244 mg) in acetone (1.7 ml). After 26 h toluene (5 ml) was added, the mixture evaporated to dryness, and the residue crystallised from acetone to give the *thioester* (22) (185 mg, 59%). Recrystallisation gave material with m.p. 144—148 °C, $[\alpha]_D$ +19° (*c* 0.282, THF); $\nu_{max.}$ (Nujol) 1 730s, 1 685s, 1 420w, 1 290m, 1 275m, 1 205s, 1 160s, 1 150s, 1 115m, 1 100m, 1 075m, 1 025w, 960w, 870w, 850m, 808w, 770w, 760m, 738m, 705m, 698m, 665w, and 640w cm^{-1}; $\lambda_{max.}$ (THF) 212 (ε 24 000) and 245sh nm (6 800); τ[$(CD_3)_2CO$] 2.67 (10 H, m, aryl-H), 4.24, 4.47, 4.80, 5.31 (2 H, 4 s, 3-H, 5-H), 5.52, 5.55, 5.6, 5.63, 5.7, 5.73, 5.77, 5.81 (2 H, 2 AB q, *J* 17 Hz, aryl-CH_2), 5.72, 5.73 (2 H, 2 s, aryl-CH_2), 6.46, 6.53 (3 H, 2 s, OMe), 8.51 8.57, and 8.62 (6 H, 3 s, 2-Me_2); *m/e* 534 [*M* − MeOH]$^+$, 443, 415, 383, 369, 324, 237, 222, 218, 202, 177, 170, 166, 142, 118, and 91 (M^+ absent) (Found: C, 55.25; H, 4.45; N, 4.95; S, 11.2. $C_{26}H_{25}F_3N_2O_5S_2$ requires C, 55.1; H, 4.45; N, 4.95; S, 11.3%).

Reaction of Adduct (14a) *and Peracetic Acid.*—Peracetic acid (0.045 ml, 1.05 equiv. oxidant) was added to adduct (14a) (83.8 mg) in dry THF (2.0 ml) and the mixture stirred overnight. Ethyl acetate was added and the solution washed twice with water, dried, and solvent evaporated off to leave an unstable oil (105 mg) [containing 1 major and 2 minor components (t.l.c., ethyl acetate–light petroleum (1 : 4)]; $\nu_{max.}$ ($CHCl_3$) 3 400—2 500m,br, 1 825s, 1 730—1 690s,br, 1 370m, 1 135s, and 1 100—1 000m,br cm^{-1}; $\lambda_{max.}$ (THF) 286 nm (ε 21 000); τ($CDCl_3$) 2.3, 2.7 (aryl-H), 3.35, 3.47 (2 s, vinyl-H), 4.66, 5.28, 6.48 (broad peaks), 8.2, 8.45, 8.55, and 8.6 (methyl peaks); *m/e* 444 (M^+), 270, 202, 136, 118, and 91. The product decomposed on attempted purification by rapid chromatography. Reaction of adduct (14a) and 3-chloroperbenzoic acid, or with excess of peracetic acid, gave the same product (t.l.c., n.m.r.).

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