Studies related to Penicillins and Cephalosporins. Part 6.[1] Synthesis of the (±)-Dinorpenicillin-spirocyclopentane System

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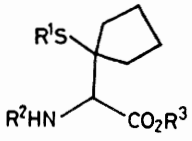
Diphenylmethyl and benzyl esters of (±)-6-azido-3-carboxypenam-2-spirocyclopentanes (18) and (20)—(23) have been obtained in a multi-step synthesis from 2-amino-2-(1-mercaptocyclopentyl)acetic acid (1). The penam backbone was completed through the formation of the 1,5-bond in a reductive annulation of chlorosulphenyl chlorides (14)—(17) with tin(II) chloride. The parent non-fused β-lactams (8)—(11) were prepared from diphenylmethyl or benzyl [1-(*p*-methoxybenzylthio)cyclopentyl]-2-[(methylthio)methylimino]acetate, (6) or (7), azidoacetyl chloride, and triethylamine. When (6) was used in this reaction, the 2-methylthio-3-azidoacetylthiazolidine-5-spirocyclopentanecarboxylic ester (12) and diphenylmethyl 2-azidoacetylamino-2-[(1-*p*-methoxybenzylthio)cyclopentyl]acetate (13) were isolated as by-products.

ALTHOUGH the synthesis of nuclear analogues of β-lactam antibiotics has been the subject of extensive research efforts,[2-5] only a few analogues of pencillin in which the methyl groups at the C-2 position are replaced by other substituents have been reported. Derivatives in which either or both methyl groups are brought to higher oxidation state have been obtained from pencillins.[6-11] Nor-[12] and dinor-penicillins[13] as well as modified compounds in which both methyl groups are replaced by ethyl groups[14] or by a polymethylene ring,[15-18] have been prepared by total synthesis. The synthesis of penam-2-cyclobutanes and -cyclopentanes was accomplished by Vanderhaeghe *et al.*[17] by cycloaddition of azidoacetyl chloride to a suitable 2-thiazoline-4-carboxylic ester according to Bose's method.[19] Dinorpenicillin-2-spirocyclobutanes, as well as the cyclopentane and cyclohexane homologues, were also prepared by Leclerq *et al.*[18] using Sheehan's classical method.[20] In the present paper we describe the synthesis of (±)-6-azidodinorpenicillanate-2-spirocyclopentanes by a route which is based on the formation of the thiazolidine ring of the penam backbone by reductive annulation of the intermediate chlorosulphenyl chlorides (14)—(17).[21]

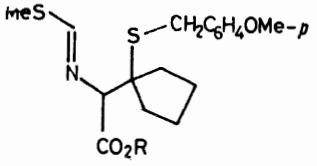
RESULTS AND DISCUSSION

These reactive non-fused β-lactams were prepared from (±)-2-amino-2-(1-mercaptocyclopentyl)acetic acid (1) in six steps. Treatment of the β-mercapto-α-amino-acid (1) with sodium and *p*-methoxybenzyl chloride in liquid ammonia gave the *S*-protected derivative (2) (87%) which was condensed with *O*-ethyl thioformate to give the thioformamide (3) (94%). Esterification with diphenyldiazomethane in acetone afforded compound (4) (quantitative). Treatment of the thioamide (4) with methyl iodide and potassium carbonate in acetone gave the (methylthio)methylimino-compound (6) (96%). This is a crystalline compound which, probably due to its bulky substituents, appears to be considerably more stable than corresponding compounds derived from other α-amino-acid esters.[22,23]

The reaction of the (methylthio)methylimino-compound (6) and azidoacetyl chloride in the presence of triethylamine gave, in addition to the expected β-lactams (8) (30%) and (10) (25%), two diastereoisomers of the *N*-azidoacetylthiazolidine (12) (10% and 11%), and the azidoacetamide (13) (15%). When the reaction was repeated with 2,6-lutidine instead of triethylamine only traces of the β-lactams (8) and (10) were detected (t.l.c.),



(1) $R^1 = R^2 = R^3 = H$
(2) $R^1 = p\text{-}MeOC_6H_4CH_2$, $R^2 = R^3 = H$
(3) $R^1 = p\text{-}MeOC_6H_4CH_2$, $R^2 = S{=}CH$, $R^3 = H$
(4) $R^1 = p\text{-}MeOC_6H_4CH_2$, $R^2 = S{=}CH$, $R^3 = CHPh_2$
(5) $R^1 = p\text{-}MeOC_6H_4CH_2$, $R^2 = S{=}CH$, $R^3 = CH_2Ph$

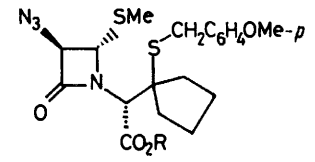


(6) $R = CHPh_2$
(7) $R = CH_2Ph$

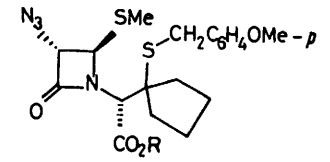
while the thiazolidines (12) were obtained in 47% yield and the azidoacetamide (13) in 23% yield.

The formation of the thiazolidines (12) is in accordance with the mechanism postulated for the reaction of acid chlorides and tertiary amines with imines which usually yields β-lactams.[24-26] In some instances evidence was given in favour of a pathway involving the formation of a keten from the acid chloride and triethylamine, and subsequent cycloaddition of the keten to the C=N bond.[25] In other cases it was shown that the adducts obtained by the interaction of acid chlorides with imines may, on addition of a tertiary amine, undergo ring-closure to β-lactams.[25,26] Accordingly, the (methylthio)methylimino-compound (6), which is represented in the Scheme by the partial structure I, may be transformed into a dipolar intermediate of type II and/or into the acyliminium

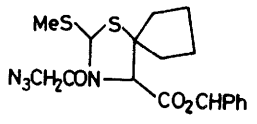
adduct IV. Both of these intermediates may undergo ring-closure (arrows *a*) to give the β-lactam III. The formation of the β-lactam requires a strong base like triethylamine, either to form the azidoketen or to abstract a proton from IV. Discrimination between these two pathways is complicated by the possible interconversion of the species I, II, and IV. However, the formation of the by-products (12) suggests that an intermediate like IV is involved. A nucleophilic attack of the sulphur atom on the partially positively charged carbon atom (arrow *b*) results in the formation of the cyclic sulphonium salt V, which loses *p*-methoxybenzyl chloride to give the thiazolidine VI. The transformation of IV into VI does not require a strong base. Indeed, compounds (12) were obtained as the major products when triethylamine was replaced by 2,6-lutidine. This hindered base was added to the reaction mixture to avoid the build-up of acidic conditions due to the possible formation of hydrogen chloride in secondary reactions. The azidoacetamide (13) may be obtained by hydrolysis of IV and/or II.



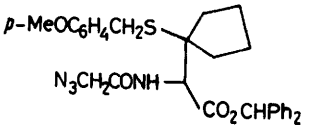
(8) *R = $CHPh_2$
(9) *R = CH_2Ph



(10) *R = $CHPh_2$
(11) *R = CH_2Ph



(12)

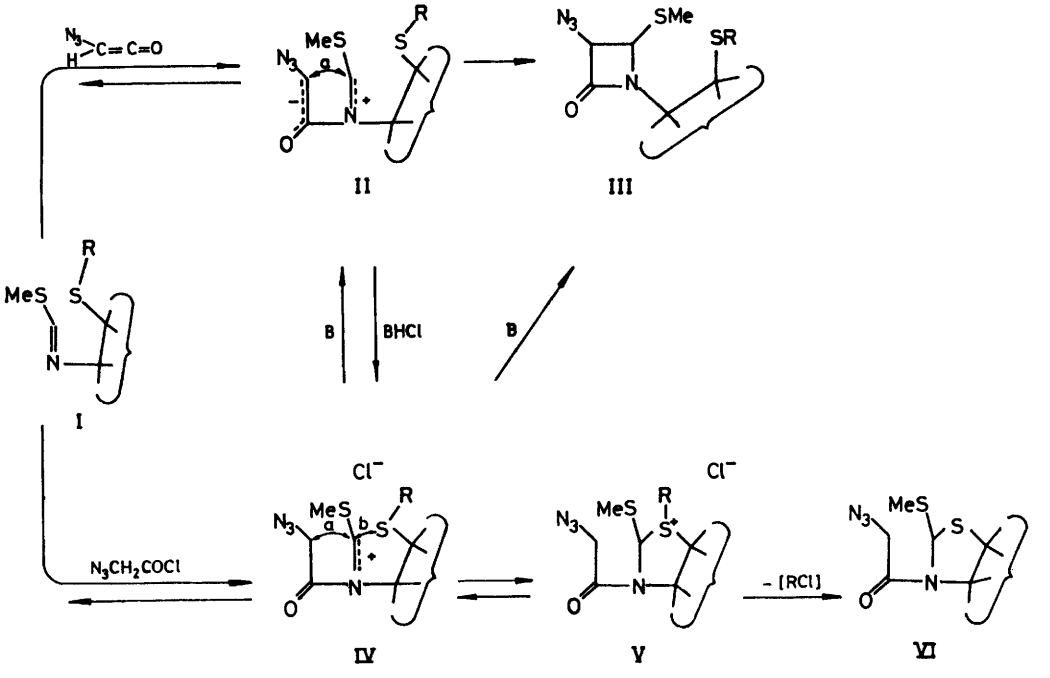


(13)

* All chiral compounds in this work consist of racemic mixtures; for simplicity, only one enantiomer of each pair has been displayed in the formulae.

Simultaneous regiospecific chlorinolysis [1] of the two sulphide groups in the β-lactams (8) and (10) afforded the corresponding chlorosulphenyl chlorides (14) and (16) as mixtures of epimers at the azetidinone C-3 position. Reductive cyclization of (14) with tin(II) chloride [27] afforded (3*SR*,5*RS*,6*RS*)-6-azido-3-diphenylmethoxycarbonylpenam-2-spirocyclopentane (18) [20% from (8)] and the (3*SR*,5*SR*,6*RS*)-isomer (20) [23% from (8)], while a similar annulation of the chlorosulphenyl chloride (16) afforded the (3*SR*,5*RS*,6*SR*)-isomer (22) [23% from (10)]. The stereochemical assignment of the three isomeric penams (18), (20), and (22) is based on the n.m.r. data of their C-3, C-5, and C-6 protons.[28]

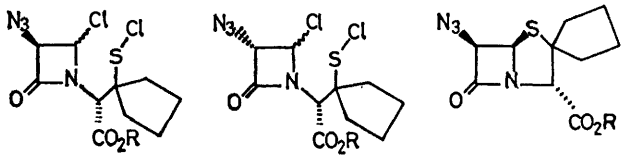
Using the same synthetic method the thioformamide (3) was converted *via* the benzyl ester (5) into the thioformimidate (7), which reacted with azidoacetyl chloride and triethylamine to give the two diastereoisomeric nonfused β-lactams (9) and (11). Regiospecific chlorinolysis of the two sulphide groups in the β-lactam (9) afforded the chlorosulphenyl chloride (15) which upon reductive cyclization yielded the *trans*-azido-β-lactam (21); the *cis*-isomer (19) was not isolated. Controlled chlorinolysis of the β-lactam (11) gave the dichloro-compound (17),



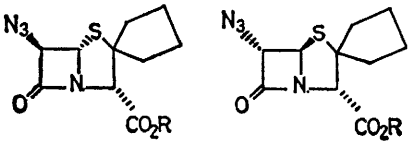
R = *p*-$MeOC_6H_4CH_2$

SCHEME

which upon treatment with tin(II) chloride afforded (3*SR*,5*RS*,6*SR*)-6-azido-3-benzyloxycarbonylpenam-2-spirocyclopentane (23). The same compound has



(14) R = $CHPh_2$ (16) R = $CHPh_2$ (18) R = $CHPh_2$
(15) R = CH_2Ph (17) R = CH_2Ph (19) R = CH_2Ph



(20) R = $CHPh_2$ (22) R = $CHPh_2$
(21) R = CH_2Ph (23) R = CH_2Ph

recently been obtained by an alternative synthetic route and subsequently converted into the (±)-spirocyclopentane analogue of penicillin V.[17]

EXPERIMENTAL

2-Amino-2-[(1-p-methoxybenzylthio)cyclopentyl]acetic Acid (2).—To a stirred suspension of 2-amino-2(1-mercaptocyclopentyl)acetic acid hydrochloride (1) [29] (25.4 g, 0.12 mol) in liquid ammonia (500 ml), small chips of sodium (8.25 g, 0.36 mol) were added. After dissolution of the sodium, *p*-methoxybenzyl chloride (18.8 g, 0.12 mol) was added dropwise during 30 min. The mixture was stirred for an additional 30 min and the ammonia was left to evaporate. The residue was dissolved in dilute sodium hydroxide and washed with ether. The aqueous solution was cooled to 0 °C and brought to pH 7.5 with 3N hydrochloric acid. After 1 h the precipitate was filtered off and dried to give *2-amino-2-[(1-p-methoxybenzylthio)cyclopentyl]acetic acid* (2) (30.7 g, 87%), m.p. 178 °C; δ (D_2O–NaOD) 1.6 (8 H, br m, $[CH_2]_4$), 3.37 (1 H, s, $NCHCO_2$), 3.51 (5 H, SCH_2 and OMe), 6.72 (2 H, d, *J* 8.5 Hz, Ar-H), and 7.16 (2 H, d, *J* 8.5 Hz, Ar-H) (Found: C, 61.15; H, 7.15; N, 4.5; S, 11.0. $C_{15}H_{21}NO_3S$ requires C, 61.00; H, 7.17; N, 4.74; S, 10.84%).

2-(1-p-Methoxybenzylthiocyclopentyl)-2-(thioformamido)-acetic Acid (3).—A stirred suspension of 2-amino-2-[(1-*p*-methoxybenzylthio)cyclopentyl]acetic acid (2) (29.5 g, 0.1 mol) in dry chloroform (800 ml) was cooled under argon. Hydrogen sulphide was bubbled in during 15 min, followed by triethylamine (21.1 g, 0.21 mol) and *O*-ethylthioformate (28.8 g, 0.32 mol). The reaction mixture was stirred under argon for 16 h and then evaporated. The residue was stirred with ice-cold water–ethyl acetate and then acidified (pH 3) with 3N hydrochloric acid. The organic fraction was washed with water, dried, and evaporated to give *2-[(1-p-methoxybenzylthio)cyclopentyl]-2-(thioformamido)acetic acid* (3) (32 g, 94%), m.p. 120 °C (from methylene dichloride–chloroform–hexane); δ ($CDCl_3$) 1.8 (8 H, br m, $[CH_2]_4$), 3.66 (2 H, s, SCH_2), 3.75 (3 H, s, OMe), 5.38 (1 H, d, *J* 8.5 Hz, $NCHCO_2$), 6.82 (2 H, d, *J* 9 Hz, Ar-H), 7.13 (2 H, d, *J* 9 Hz, Ar-H), 8.2 (br, CO_2H), 8.55 br m, NH), and 9.48 (1 H, d, *J* 6 Hz, HCS); *m/e* 339 (M^+) (Found: C, 56.45; H, 6.2; N, 4.3; S, 18.75. $C_{16}H_{21}NO_3S_2$ requires C, 56.63; H, 6.24; N, 4.13-S, 18.86%).

Diphenylmethyl 2-[(1-p-Methoxybenzylthio)cyclopentyl]-2-(thioformamido)acetate (4).—To a stirred solution of 2-[(1-*p*-methoxybenzylthio)cyclopentyl]-2-(thioformamido)acetic acid (3) (33.9 g, 0.1 mol) in acetone (250 ml), diphenyldiazomethane in acetone was added dropwise until no more acid remained in the reaction mixture. Evaporation followed by recrystallization from methylene dichloride–hexane afforded *diphenylmethyl 2-[(1-p-methoxybenzylthio)cyclopentyl]-2-(thioformamido)acetate* (4) (50.0 g, quantitative), m.p. 101 °C; $\nu_{max.}$ (film) 1 740, 1 605, 1 590, and 1 510 cm^{-1}; δ ($CDCl_3$) 1.8 (8 H, br m, $[CH_2]$), 3.31 (2 H, s, SCH_2), 3.77 (3 H, s, OMe), 5.55 (1 H, d, *J* 8.5 Hz, $NCHCO_2$), 6.78 (2 H, d, *J* 9 Hz, Ar-H), 6.98 (1 H, s, CO_2CH), 7.05 (2 H, d, *J* 9 Hz, Ar-H), 7.35 (10 H, m, Ph_2C), 8.4 (1 H, br m, NH), and 9.45 (1 H, d, *J* 6 Hz, NCS) [after addition of D_2O: signal at δ 8.43 absent, 5.55 (1 H, s), and 9.45 (1 H, s)]; *m/e* 505 (M^+) (Found: C, 69.2; H, 6.2; N, 2.75; S, 12.45. $C_{29}H_{31}NO_3S_2$ requires C, 68.91; H, 6.18; N, 2.77; S, 12.66%).

Benzyl 2-[(1-p-Methoxybenzylthio)cyclopentyl]-2-(thioformamido)acetate (5).—To a stirred solution of 2-[(1-*p*-methoxybenzylthio)cyclopentyl]-2-(thioformamido)acetic acid (3) (23.0 g, 67.8 mmol) in ether (200 ml), benzyldiazomethane in ether was added dropwise until no more acid remained (t.l.c.). Evaporation followed by silica gel chromatography (hexane–acetone) gave benzyl-2-[(1-*p*-methoxybenzylthio)cyclopentyl]-2-(thioformamido)acetate (5) (20 g, 68%); $\nu_{max.}$ ($CHCl_3$), 3 330, 1 735, and 1 500 cm^{-1}; δ ($CDCl_3$), 1.6—2.0 (8 H, m, $[CH_2]_4$), 3.48 (2 H, s, SCH_2), 3.72 (3 H, s, OMe), 5.19 (2 H, s, CH_2Ph), 5.44 (1 H, d, *J* 9 Hz, $NCHCO_2$), 6.77 (2 H, d, *J* 9 Hz, Ar-H), 7.33 (2 H, d, *J* 9 Hz, Ar-H), 7.46 (5 H, s, Ph), 8.3 (br, 1 H, NH), and 9.36 (1 H, d, *J* 5 Hz, HCS).

Diphenylmethyl 2-[(1-p-Methoxybenzylthio)cyclopentyl]-2-[(methylthio)methylimino]acetate (6).—To a mixture of diphenylmethyl 2-[(1-*p*-methoxybenzylthio)cyclopentyl]-2-(thioformamido)acetate (4) (20.2 g, 40.0 mmol) and potassium carbonate (5.86 g, 42.5 mmol) in dry acetone (240 ml), methyl iodide (7.28 g, 51.3 mmol) was added. The mixture was vigorously stirred at room temperature for 24 h, and then additional portions of methyl iodide (1.47 g, 10.4 mmol) and of potassium carbonate (1.10 g, 8.0 mmol) were added and stirring was continued for an additional 16 h. The mixture was filtered and evaporated, and the residue was dissolved in methylene dichloride and filtered. The solvent was removed and the residue crystallized from acetone–hexane to give *diphenylmethyl 2-[(1-p-methoxybenzylthio)cyclopentyl]-2-[(methylthio)methylimino]acetate* (6) (20.0 g, 96%), m.p. 116 °C; $\nu_{max.}$ ($CHCl_3$) 1. 740, 1 605, and 1 590 cm^{-1}; δ ($CDCl_3$) 1.8 (8 H, br m, $[CH_2]_4$), 2.37 (3 H, s, SMe), 3.73 (5 H, apparent s, OMe and SCH_2), 4.32 (1 H, s, $NCHCO_2$), 6.78 (2 H, d, *J* 8.5 Hz, Ar-H), 7.00 (1 H, s, $CHPh_2$), 7.13 (2 H, d, *J* 8.5 Hz, Ar-H), 7.35 (10 H, m, CPh_2), and 8.32 (1 H, s, N=CH–S); *m/e* 519 (M^+) (Found: C, 69.6; H, 6.40; N, 2.7; S, 12.05. $C_{30}H_{33}NO_3S_2$ requires C, 69.35; H, 6.39; N, 2.69; S, 12.32%).

Reaction of Compound (6) *with Azidoacetyl Chloride and Triethylamine.*—Compound (6) (5.19 g, 10.0 mmol) and triethylamine (3.00 g, 29.0 mmol) were dissolved in dry toluene (250 ml). A solution of azidoacetyl chloride (3.22 g, 27 mmol) in dry toluene (250 ml) was added, under argon, during 8 h with stirring. The mixture was stirred for an

additional 20 h, filtered through Celite, and evaporated. Column chromatography of the residue on silica gel using acetone–hexane as eluant afforded four fractions: (*a*) The less-polar *isomer* of the thiazolidine (12) (0.50 g, 10.4%), m.p. 132 °C (methylene dichloride–hexane); $\nu_{max.}$ ($CHCl_3$) 2 110, 1 740, and 1 670 cm^{-1}; δ ($CDCl_3$) 1.3—2.2 (8 H, m, $[CH_2]_4$), 2.22 (3 H, br s, SMe), 4.5—5.0 (3 H, m, N_3CH_2CO and $NCHCO_2$), 6.05br (1 H, MeSC*H*N), 6.97 (1 H, s, CO_2CH), and 7.37 (10 H, CPh_2) (Found: C, 59.5; H, 5.5; N, 11.4; S, 13.1. $C_{24}H_{26}N_4O_3S_2$ requires C, 59.7; H, 5.4; N, 11.6; S, 13.3%): (*b*) the more-polar *isomer* of the *thiazolidine* (12) (0.54 g, 11.2%), m.p. 160 °C (methylene dichloride–hexane); $\nu_{max.}$ ($CHCl_3$) 2 110, 1 740, and 1 670 cm^{-1}; δ ($CDCl_3$) 1.3—2.2 (8 H, m, $[CH_2]_4$), 2.23 (3 H, br s, SMe), 4.20 (2 H, br s, N_3CH_2CO), 4.90 (br, 1 H, $NCHCO_2$), 6.10 (br, 1 H, MeSC*H*N), 7.04 (1 H, s, CO_2CH), and 7.40 (10 H, CPh_2) (Found: C, 59.9; H, 6.0; N, 11.4; S, 13.6. $C_{24}H_{26}N_4O_3S_2$ requires: C, 59.7; H, 5.4; N 11.6; S, 13.3%): (*c*) an 11 : 9 mixture of the two isomeric β-lactams (8) and (10): and (*d*) the amide (13) (0.83 g, 15%); $\nu_{max.}$ ($CHCl_3$) 2 110, 1 740, 1 680, and 1 605 cm^{-1}; δ ($CDCl_3$) 1.4—2.1 (8 H, m, $[CH_2]_4$), 3.32 (2 H, s, S*CH*$_2$Ph), 3.73 (3 H, s, OMe), 3.97 (2 H, s, N_3CH_2CO), 4.87 (1 H, d, *J* 8.5 Hz, $NCHCO_2$), and 6.65—7.5 (16 H, m, NH, $CHPh_2$, C_6H_4); *m/e* 377 (M^+ — $CHPh_2$), 349 (M^+ — $CHPh_2$ — N_2), 225, and 197.

Fraction (*c*) was chromatographed on silica gel using toluene as eluant to give the β-lactam (8) (1.8 g, 30%); $\nu_{max.}$ (film) 2 100, 1 765, 1 740, and 1 610 cm^{-1}; δ ($CDCl_3$) 1.8 (br m, $[CH_2]$), 1.85 (1 H, s, SMe), 3.70 (s, SCH_2), 3.73 (s, OMe) (5 H), 4.53 (1 H, d, *J* 2 Hz, azetidine-H), 4.77 (1 H, d, *J* 2 Hz, azetidine-H), 4.85 (1 H, s, $NCHCO_2$), 6.80 (2 H, d, *J* 9 Hz, Ar-H), 6.98 (1 H, s, CO_2CH), 7.21 (2 H, d, *J* 9 Hz, Ar-H), and 7.38 (10 H, s, CPh_2); *m/e* 602 (M^+), 574 (M^+ — N_2): this was followed by the β-lactam (10) (1.5 g, 25%); $\nu_{max.}$ (film) 2 100, 1 765, 1 740 and 1 610 cm^{-1}; δ ($CDCl_3$) 1.8 (br m, $[CH_2]_4$), 1.77 (3 H, s, SMe), 3.68 (2 H, s, SCH_2), 3.78 (3 H, s, OMe), 4.43 (d, *J* 2 Hz, azetidine-H and 1 H, s, $NCHCO_2$), 4.58 (1 H, d, *J* 2 Hz, azetidine-H), 6.83 (2 H, d, *J* 9 Hz, Ar-H), 6.98 (1 H, s, C*H*Ph_2), 7.21 (2 H, d, *J* 9 Hz, Ar-H), and 7.38 (10 H, s, CPh_2; *m/e* 434 (M^+ — CH_2Ph_2), 406 (M^+ — CH_2Ph_2 — N_2).

(3SR,5RS,6RS)-6-*Azido*-3-*diphenylmethoxycarbonylpenam*-2-*spirocyclopentane* (18) *and* (3SR,5SR,6RS)-6-*Azido*-3-*diphenylmethoxycarbonylpenam*-2-*spirocyclopentane* (20).—To a stirred solution of the β-lactam (8) (1.7 g, 2.8 mmol) in dry methylene dichloride (60 ml) under argon at 0 °C, a solution of chlorine in dry carbon tetrachloride (66 ml, 0.092M) was added during 30 min. After an additional 15 min at 0 °C the solution was evaporated to give the dichloro-compound (14); $\nu_{max.}$ (film) 2 115, 1 790, 1 740, and 1 610 cm^{-1}. The crude compound was dissolved in dry dioxan (85 ml) and treated with anhydrous tin(II) chloride (580 mg, 3.06 mmol) for 40 h at room temperature. The mixture was treated with hydrogen sulphide at 0 °C and then filtered through a short silica gel column. A second portion of inorganic salt was removed by evaporation of the filtrate, dissolution in chloroform, and filtration through a short silica gel column. Evaporation of the filtrate followed by chromatography on silica gel, using toluene–ethyl acetate as eluant, afforded a mixture of two β-lactams which on chromatography on silica gel using benzene as eluant gave the 6-β-*azidopenam* (18) (242 mg, 20%); $\nu_{max.}$ ($CHCl_3$) 2 110, 1 780, and 1 740 cm^{-1}; δ ($CDCl_3$) 1.8br (8 H, br m, $[CH_2]_4$), 4.71 (1 H, s, 3-H), 4.91 (1 H, d, *J* 4 Hz, azetidine-H), 5.49 (1 H, d, *J* 4 Hz, azetidine-H), 6.98 (1 H, s, CO_2CH), and 7.37 (10 H, s, CPh_2); *m/e* 406 (M^+ — N_2), 352 (M^+ — N_3CHCO) (Found: C, 63.2; H, 5.0. $C_{23}H_{22}N_4O_3S$ requires C, 63.6; H, 5.1%): followed by the 6-β-*azido*-5-epi-*penam* (20) (280 mg, 23%), m.p. 127 °C (methylene dichloride–hexane); $\nu_{max.}$ (film) 2 115, 1 790, and 1 740 cm^{-1}; δ ($CDCl_3$) 1.8 (8 H, br m, $[CH_2]_4$), 3.95 (1 H, s, 3-H), 4.68 (1 H, d, *J* 2 Hz, azetidine-H), 4.95 (1 H, d, *J* 2 Hz, azetidine-H), 7.0 (1 H, s, CO_2CH), and 7.35 (10 H, s, CPh_2; *m/e* 406 (M^+ — N_2) (Found: C, 63.5; H, 5.0; N, 12.7; S, 7.0. $C_{23}H_{22}N_4O_3S$ requires C, 63.6; H, 5.1; N, 12.9; S, 7.4%).

(3SR,5RS,6SR)-6-*Azido*-3-*diphenylmethoxycarbonyl*-*penam*-2-*spirocyclopentane*(22).—To a stirred solution of the β-lactam (10) (1.13 g, 1.9 mmol) in dry methylene dichloride (33 ml) at 0 °C, a solution of chlorine in dry carbon tetrachloride (43 ml, 0.092M) was added during 15 min. After an additional 15 min at 0 °C, the solution was evaporated to give the dichloro-compound (16), $\nu_{max.}$ (film) 2 115, 1 790, 1 740, and 1 615 cm^{-1}. The crude compound was dissolved in dry dioxan (30 ml) and treated with anhydrous tin(II) chloride (350 mg, 1.9 mmol) for 40 h and then evaporated. The residue was taken up with chloroform and filtered through a short silica gel column and evaporated. Chromatography of the residue using benzene as eluant afforded the 6-α-azidopenam (22) (190 mg, 23%); $\nu_{max.}$ (film) 2 115, 1 790, and 1 740 cm^{-1}; δ ($CDCl_3$) 1.8 (8 H, br m $[CH_2]_4$), 4.59 (1 H, d, *J* 1.5 Hz, azetidine-H), 4.75 (1 H, s, 3-H), 5.27 (1 H, d, *J* 1.5 Hz, azetidine-H), 7.0 (1 H, s, CO_2CH), and 7.37 (10 H, s, CPh_2); *m/e* 406 (M^+ — N_2) (Found: C, 63.6; H, 5.3. $C_{23}H_{22}N_4O_3S$ requires C, 63.6; H, 5.1%).

3-*Azido*-1-{*benzyloxycarbonyl*-[(1-p-*methoxybenzylthio*)-*cyclopentyl*]*methyl*}-4-(*methylthio*)*azetidin*-2-*ones* (9) *and* (11).—The thioamide (5) (15.0 g, 35 mmol) was treated with potassium carbonate and methyl iodide as described for the preparation of (6) to give compound (7); $\nu_{max.}$ ($CDCl_3$) 1 740 and 1 600 cm^{-1}; δ ($CDCl_3$) 1.80 (8 H, m, $[CH_2]_4$), 2.35 (3 H, s, SMe), 3.72 (5 H, apparent s, SCH_2 and OMe), 4.25 (1 H, s, $NCHCO_2$), 5.18 (2 H, s, CO_2CH_2), 6.74 (2 H, d, *J* 9 Hz, Ar-H), 7.15 (2 H, d, *J* 9 Hz, Ar-H), 7.32 (5 H, s, Ph), and 8.17 (1 H, s, N=CH–S). To a solution of the crude compound (7) and triethylamine (4.24 g, 42 mmol) in dry toluene (400 ml), a solution of azidoacetyl chloride (5.0 g, 41.9 mmol) in toluene (400 ml) was added with stirring during 8 h. After 20 h the reaction mixture was concentrated under reduced pressure to half its volume. A second portion of triethylamine (4.24 g, 42 mmol) was added, followed by the portionwise (8 h) addition of azidoacetyl chloride (5.0 g, 41.9 mmol) in toluene (400 ml). After stirring for an additional 20 h the mixture was filtered through Celite and evaporated. Chromatography of the residue on silica gel using toluene-ethyl acetate afforded the β-lactam (9) (5.07 g, 28%); $\nu_{max.}$ ($CHCl_3$) 2 105, 1 770, and 1 745 cm^{-1}; δ ($CDCl_3$) 1.84 (m, $[CH_2]$), and 2.04 (3 H, s, SMe), 3.72 (s, SCH_2), 3.76 (3 H, s, OMe), 4.56 (1 H, d, *J* 2 Hz, azetidine-H), 4.78 (s, $NCHCO_2$), 4.85 (1 H, d, *J* 2 Hz, azetidine-H), 6.82 (2 H, d, *J* 9 Hz, Ar-H), 7.23 (2 H, d, *J* 9 Hz, Ar-H), and 7.35 (5 H, s, Ph); *m/e* 526 (M^+), 498 (M^+ — N_2), 484 (M^+ — N_3): followed by the β-lactam (11) (2.03 g, 11%); $\nu_{max.}$ ($CHCl_3$) 2 105, 1 775, and 1 745 cm^{-1}; δ ($CDCl_3$) 1.83 (m, $[CH_2]_4$), 1.93 (3 H, s, SMe), 3.71 (s, SCH_2), 3.77 (3 H, s, OMe), 4.33 (1 H, s, $NCHCO_2$), 4.47 (1 H, d, *J* 2 Hz, azetidine-H), 4.74 (1 H, d, *J* 2 Hz, azetidine-H), 5.21 (2 H, s, CO_2CH_2), 6.82 (2 H, d, *J* 9 Hz, Ar-H), 7.23 (2 H, d, *J* 9 Hz, Ar-H), and 7.38 (5 H, s, Ph); *m/e* 526 (M^+), 498 (M^+ — N_2), 484 (M^+ — N_3).

(3SR,5SR,6RS)-6-*Azido*-3-*benzyloxycarbonylpenam*-2-*spirocyclopentane* (21).—Chlorinolysis of the β-lactam (9)

(526 mg, 1 mmol) under the conditions described for the chlorinolysis of the β-lactam (8) gave the dichloro-compound (15); $\nu_{max.}$ ($CHCl_3$) 2 115, 1 790, and 1 740 cm^{-1}; δ ($CDCl_3$) 1.9 (8 H, m, $[CH_2]_4$), 4.69 (d, J 1.5 Hz, azetidine-H), 4.70 (1 H, s, $NCHCO_2$), 5.21 (2 H, s, CO_2CH_2), 5.43 (1 H, d, J 1.5 Hz, azetidine-H), and 7.35 (5 H, s, Ph). The crude compound (9) was treated immediately with anhydrous tin(II) chloride as described above for the preparation of (20) to give the 6-β-*azido*-5-epi-*penam* (21) (100 mg, 28%); $\nu_{max.}$ ($CHCl_3$) 2 115, 1 790, and 1 740 cm^{-1}; δ ($CDCl_3$) 1.9 (8 H, m, $[CH_2]_4$), 3.88 (1 H, s, $NCHCO_2$), 4.72 (1 H, d, J 2 Hz, azetidine-H), 4.95 (1 H, d, J 2 Hz, azetidine-H), 5.21 (2 H, s, CO_2CH_2), and 7.35 (5 H, s, Ph); *m/e* 330 ($M^+ - N_2$) (Found: C, 57.2; H, 5.2; N, 15.8; S, 9.3. $C_{17}H_{18}N_4O_3S$ requires C, 57.0; H, 5.1; N, 15.6; S, 8.9%).

(3SR,5RS,6SR)-6-*Azido*-3-*benzyloxycarbonylpenam*-2-*spirocyclopentane* (23).—The β-lactam (11) was chlorinolysed as described for the chlorinolysis of (10) to give the dichloro-compound (17); $\nu_{max.}$ ($CHCl_3$) 2 110, 1 790, and 1 735 cm^{-1}. The crude dichloro-compound (17) was treated with anhydrous tin(II) chloride as described for the preparaton of (22) to give the 6-α-*azidopenam* (23) (28%); $\nu_{max.}$ ($CHCl_3$) 2 115, 1 780, and 1 740 cm^{-1}; δ ($CDCl_3$) 1.78 (8 H, m, $[CH_2]_4$), 4.59 (1 H, d, J 2 Hz, azetidine-H), 4.69 (1 H, $NCHCO_2$), 5.21 (s, CO_2CH_2), 5.24 (1 H, d, azetidine-H), and 7.37 (5 H, s, Ph) [lit.,[17] δ ($CDCl_3$) 1.75 (m), 4.5 (d, J 1.5 Hz), 4.6 (s), 5.1 (s), 5.17 (d, J 1.5 Hz), and 7.3]; *m/e* 330 ($M^+ - N_2$) (Found: C, 56.75; H, 5.0; N, 12.25. $C_{17}H_{18}N_4O_3S$ requires C, 57.0; H, 5.1; N, 15.6%).

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