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Studies Related to Penicillins and Cephalosporins. Part II.[1] An Approach to the Synthesis of β-Lactam Antibiotics

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β-Lactams having a common nitrogen atom with valine methyl ester and carrying a thio-substituent at the 4-position have been prepared by the reaction of alkyl *N*-(1-methoxycarbonyl-2-methylpropyl)thioformimidates with a keten, or with an acid chloride and triethylamine. *cis*-3-Azido-4-benzylthio-1-(1-methoxycarbonyl-2-methylpropyl)-azetidin-2-one (21) was obtained by displacement of the chlorine atom in *trans*-4-benzylthio-3-chloro-1-(1-methoxycarbonyl-2-methylpropyl)azetidin-2-one (20) by azide ion. Subsequent reduction with zinc in acetic acid afforded the corresponding *cis*-3-amino-4-benzylthio-β-lactam (22). These azetidin-2-ones represent a class of new synthetic compounds which may serve as intermediates in the synthesis of β-lactam antibiotics.

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THE antibiotic activity of penicillins (1) and cephalosporins (9) is attributed to their inhibiting effect on the synthesis of bacterial cell walls.[2] Although the whole complex of requirements necessary for antimicrobial activity has not been fully established, it is remarkable that most[3] of the known β-lactam antibiotics are bicyclic and contain the partial structure (10).[4] In a new scheme for the synthesis of potential antibiotics having this partial structure, we have suggested the idea of constructing a β-lactam ring on the nitrogen atom of an α-amino-acid.[1] This method should enable the conversion of natural and synthetic α-amino-acids, through their thioformimidate derivatives (11), into monocyclic β-lactams of type (12) where X represents an amino- or a potential amino-group. A rational combination of the functional groups included in the side chain R^2 of the α-amino-acid systems and of the sulphur-protecting groups R^1 would give β-lactams (12) that might eventually be converted by ring closure on the sulphur atom into penicillins and cephalosporins with modified nuclei as well as into the natural antibiotics themselves.

Staudinger's[5] method for the preparation of β-lactams by the reaction of oxo-ketens with imines has been developed and modified in connection with the investigation of penicillin synthesis.[6] Sheehan and Ryan[7] introduced the use of acid chlorides and tertiary amines for the preparation of β-lactams from imines and 2-substituted thiazolines. Although this reaction does not necessarily involve a keten intermediate[8] the product is identical with that expected of a formal cycloaddition of a formyl keten and an imine. This method has been subsequently applied to other compounds bearing a carbon–nitrogen double bond, *e.g.* imidates,[9,10] thioimidates,[9] 2-aryl-5,6-dihydro-1,3-oxazines,[11] and various dihydrothiazines.[12] Recently[13] 6-*epi*-aminopenicillanic ester (2) was synthesised by the reaction between methyl 5,5-dimethyl-Δ^2-thiazoline-4-carboxylate and azidoacetyl chloride in the presence of triethylamine, followed by hydrogenation of the resulting azido-bicyclic-β-lactam (3). This synthesis led, however, exclusively to the biologically inactive 5,6-*trans*-isomer.

The applicability of this method to the synthesis of β-lactams of type (12) was studied with the valine derivatives (14) and (15) as model compounds. Condensation of L-valine methyl ester with *O*-ethyl thioformate afforded *N*-thioformyl-L-valine methyl ester (13) (76%). Treatment of compound (13) with sodium hydride in an inert solvent followed by alkylation with methyl iodide gave methyl *N*-(1-methoxycarbonyl-2-methylpropyl)thioformimidate (14) (84%). The benzyl thioformimidate (15) was obtained (85%) in the same way by use of benzyl bromide. Acidic hydrolysis of the thioimidate (14) afforded optically pure L-valine methyl ester hydrochloride, thus proving that the preparation of (14) did not involve any appreciable racemisation.

In order to test the reactivity of these thioformimidates they were first treated with diphenylketen, which is one of the most powerful ketens for the preparation of β-lactams.[6] On addition of diphenylketen in toluene to the thioimidates (14) and (15) in the same solvent, the respective β-lactams (16) (47%) and (17) (69%) were obtained. The n.m.r. spectra indicate that each of these consists of a mixture of two diastereoisomers. β-Lactams of type (12) were then prepared by treatment of the thioimidates and triethylamine

[1] Preliminary report, M. D. Bachi and O. Goldberg, *J.C.S. Chem. Comm.*, 1972, 319; Part I, M. D. Bachi and M. Rothfield, preceding paper.

[2] D. J. Tipper and J. L. Strominger, *Proc. Nat. Acad. Sci. U.S.A.*, 1965, **54**, 1133; *J. Biol. Chem.*, 1968, **243**, 3169; E. M. Wise, jun., and J. T. Park, *Proc. Nat. Acad. Sci. U.S.A.*, 1965, **54**, 75; K. Izaki, M. Matsuhashi, and J. L. Strominger, *J. Biol. Chem.*, 1968, **243**, 3180.

[3] Two β-lactam antibiotics having an additional substituent on the ring have been recently discovered; R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgens, M. M. Hoehn, W. M. Stark, and J. G. Whitney, *J. Amer. Chem. Soc.*, 1971, **93**, 2308.

[4] For a recent discussion of structure–activity relationship, see R. M. Sweet and L. F. Dahl, *J. Amer. Chem. Soc.*, 1970, **92**, 5489.

[5] H. Staudinger, *Annalen*, 1907, **356**, 51.

[6] J. C. Sheehan and E. J. Corey, *Org. Reactions*, 1957, **9**, 388.

[7] J. C. Sheehan and J. J. Ryan, *J. Amer. Chem. Soc.*, 1951, **73**, 1204, 4367.

[8] A. K. Bose, G. Spiegelman, and M. S. Manhas, *Tetrahedron Letters*, 1971, 3167.

[9] L. Paul, A. Draeger, and G. Hilgetag, *Chem. Ber.*, 1966, **99**, 1957.

[10] A. K. Bose, B. Anjaneyulu, S. Bhattacharya, and M. S. Manhas, *Tetrahedron*, 1967, **23**, 4769.

[11] J. C. Sheehan and M. Dadíc, *J. Heterocyclic Chem.*, 1968, **5**, 779.

[12] L. Paul, P. Polczynski, and G. Hilgetag, *Chem. Ber.*, 1967, **100**, 2761; A. K. Bose, V. Sudarsanam, B. Anjaneyulu, and M. S. Manhas, *Tetrahedron*, 1969, **25**, 1191.

[13] A. K. Bose, G. Spiegelman, and M. S. Manhas, *J. Amer. Chem. Soc.*, 1968, **90**, 4506.

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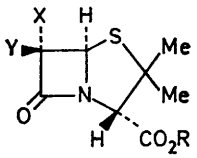
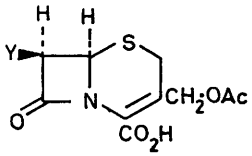
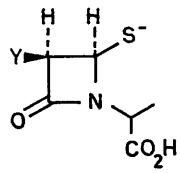
with phthaloylglycyl chloride in methylene dichloride or toluene. The thioimidates (14) and (15) gave the respective β-lactams (18) (40%) and (19) (39%). The n.m.r. spectrum of (18) in deuteriochloroform displays



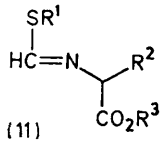
(1) R = H, X = H, Y = acylamino
(2) R = Me, X = NH_2, Y = H
(3) R = Me, X = N_3, Y = H
(4) R = Me, X = Cl, Y = H
(5) R = CH_2Ph, X = $O{\cdot}SO_2Me$, Y = H
(6) R = Me, X = Br, Y = H
(7) R = CH_2Ph, X = OMe, Y = Br
(8) R = CH_2Ph, X = Br, Y = OMe



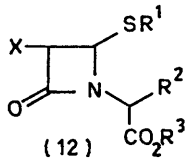
(9) Y = acylamino



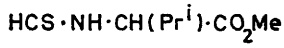
(10) Y = acylamino



(11)



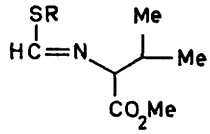
(12)



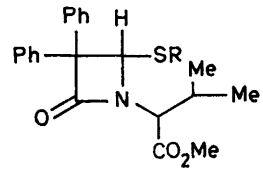
(13)

for the two β-lactam ring protons three doublets (J 2·5 Hz) centred at δ 5·09, 5·15, and 5·34 p.p.m. (ratio 1 : 1 : 2), whereas in deuteriobenzene it displays four doublets (J 2·6 Hz) at 5·10, 5·15 (1H) and 5·44, 5·47 (1H). The coupling constants of vicinal protons in β-lactams have been used to distinguish between *cis*- and *trans*-isomers. The reported range for monocyclic β-lactams is 1·5—2·8 Hz for *trans*-β-lactams and 4·5—5·9 Hz for *cis*-β-lactams.[10,14] It was therefore concluded that compound (18) consists of a 1 : 1 mixture of two diastereoisomeric *trans*-β-lactams whose ring protons exhibit two partially superimposable AB patterns. Similarly the n.m.r. spectrum of (19) displays two partially overlapping AB patterns characteristic for two *trans*-β-lactams: δ(C_6D_6) 5·17, 5·23, 5·39, and 5·41 (all d, J 2·6 Hz). It has been suggested[10] that the sequence of addition of the reactants influences the stereochemistry of the 3-azido-β-lactam products of type (23). Thus 'the slow addition of azidoacetyl chloride to a solution of benzalaniline and triethylamine in methylene chloride favours the *cis*-product, while the *trans*-stereochemistry is favoured when triethylamine is added to a mixture of the Schiff base and azidoacetyl chloride.'[10] It seems however that this kind of steric control does not apply to the formation of β-lactams from the thioformimidates (14) and (15), as the *trans*-diastereoisomers (18) and (19) were exclusively formed. Since the *cis*-stereochemistry is essential for the antibacterial activity of β-lactams, an indirect route to the *cis*-isomers was developed.

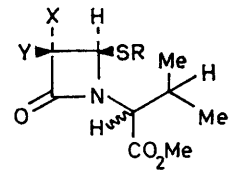
A solution of the thioformimidate (15) and triethylamine in toluene was treated with chloroacetyl chloride to give the chloro-β-lactam (20) (45%). N.m.r. spectroscopy revealed the presence of a 5 : 3 mixture of two *trans*-diastereoisomers, subsequently separated by column chromatography on Florisil. The n.m.r. signals for the ring protons consist of doublets at δ(C_6D_6) 4·38 and 4·55 p.p.m. (J 1·9 Hz) for the first-eluted compound and at 4·33 and 4·68 (J 1·7 Hz) for the second. A mixture of the two *trans*-diastereoisomers (20) was warmed in dimethyl sulphoxide with an excess of



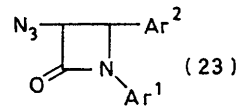
(14) R = Me
(15) R = CH_2Ph



(16) R = Me
(17) R = CH_2Ph



(18) R = Me, X = phthalimido, Y = H
(19) R = CH_2Ph, X = phthalimido, Y = H
(20) R = CH_2Ph, X = Cl, Y = H
(21) R = CH_2Ph, X = H, Y = N_3
(22) R = CH_2Ph, X = H, Y = NH_2



(23)

sodium azide, yielding, after chromatography on Florisil, equal amounts of the two *cis*-diastereoisomeric

[14] H. B. Kagan, J. J. Basselier, and J. L. Luche, *Tetrahedron Letters*, 1964, 941; J. L. Luche, H. B. Kagan, R. Parthasarathy, G. Tsoucaris, C. De Rango, and C. Zelwer, *Tetrahedron*, 1968, **24**, 1275; K. D. Barrow and T. M. Spotswood, *Tetrahedron Letters*, 1965, 3325; F. Duran and L. Ghosez, *ibid.*, 1970, 245; L. D. Hatfield, J. Fisher, F. L. Jose, and R. D. G. Cooper, *ibid.*, p. 4897; D. A. Nelson, *ibid.*, 1971, 2543.

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azido-β-lactams (21) (25%) and a 1 : 1 diastereoisomeric mixture of the starting material (20) (54%). The n.m.r. spectrum of the first-eluted isomer (21) displays the characteristic[10,14] AB pattern: $\delta(C_6D_6)$ 3·96 (d) and 4·81 (d) (J 4·7 Hz) and that of the second shows $\delta(C_6D_6)$ 3·98 (d) and 4·40 (d) (J 5·0 Hz). Similar diastereoisomeric mixtures of the product and the starting material were obtained when the reaction was performed with one of the isomers (20). These results indicate that a nucleophilic substitution with inversion of configuration occurs at C-3 of the β-lactam ring while racemisation takes place at the α-carbon atom of the valine system. Use of dimethylformamide instead of dimethyl sulphoxide as the reaction medium resulted in a lower yield (11%).

Previous attempts to perform similar nucleophilic substitutions in methyl 6α-chloropenicillanate (4),[15] in benzyl 6α-methylsulphonyloxypenicillanate (5),[16] and in methyl 6α-bromopenicillanate (6)[17] resulted in the cleavage of the β-lactam ring. The higher stability of (20) as compared with that of bicylic β-lactams bearing similar substituents is in accordance with the postulate that the lability of penicillins is a consequence of steric deformation of the amide bond in the penam system.[4,18] Recently substitutions of a bromine atom by an azido-group in benzyl 6β-bromo-6-methoxypenicillanate (7) and in its epimer (8) have been achieved by treatment with lithium azide in dimethylformamide.[19]

Reduction of the two azido-β-lactams (21) with zinc in 90% acetic acid afforded the respective *cis*-amino-β-lactams (22) (80%). The ring proton signals appear in the n.m.r. spectra as doublets at $\delta(C_6D_6)$ 3·91 and 4·87 p.p.m. (J 4·7 Hz) for one isomer, and at $\delta(C_6D_6)$ 4·01 and 4·56 (J 4·8 Hz) for the other.

Having demonstrated that L-valine methyl ester can be converted into β-lactams related to penicillins and cephalosporins, we are now studying the possibility of employing other compounds of type (12) as intermediates in the synthesis of bicyclic β-lactams of potential antibiotic activity.

EXPERIMENTAL

M.p.s were determined with a Büchi apparatus. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. I.r. spectra were taken on a Perkin-Elmer 237 grating spectrometer. ^{1}H N.m.r. spectra were recorded on a Varian A60 spectrometer, with tetramethylsilane as internal standard. Mass spectra were determined on an Atlas MAT CH4 instrument. Reactions were performed under nitrogen and, unless otherwise stated, in dry solvents. Evaporations were carried out with a rotary evaporator under reduced pressure.

N-Thioformyl-L-valine Methyl Ester (13).—A solution of L-valine methyl ester hydrochloride (16·75 g), triethylamine (10·12 g), and *O*-ethyl thioformate[20] (11·25 g) in chloroform (250 ml) was kept overnight at room temperature. It was then washed with N-hydrochloric acid followed by saturated sodium chloride solution, dried, and evaporated. The residue was distilled (95—105° at 0·07 mmHg) to give the *thioformyl ester* (13) (13·30 g, 76%), $[\alpha]_D^{20}$ −8° (*c* 2 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3390 and 1740 cm^{-1}, δ ($CDCl_3$) 0·99 (3H, d, J 7 Hz, CH*Me*), 1·03 (3H, d, J 7 Hz, CH*Me*), 2·0—2·4 (1H, m, C*H*Me$_2$), 3·78 (3H, s, OMe), 5·98 (1H, dd, J 5 and 9 Hz, N·C*H*·CO$_2$Me), 8·53br (1H, NH), and 9·53 (1H, d, J 6 Hz, HCS) [after treatment with D_2O: 5·28 (1H, d, J 5 Hz), 8·53 absent, and 9·53 (1H, s)] (Found: C, 48·05; H, 7·6; N, 7·9; S, 18·2. $C_7H_{13}NO_2S$ requires C, 48·0; H, 7·5; N, 8·0; S, 18·3%), *m/e* 175 (M^+).

Methyl N-(1-Methoxycarbonyl-2-methylpropyl)thioformimidate (14).—A solution of the ester (13) (875 mg) in toluene (25 ml) was added during 30 min to an ice-cold stirred suspension of sodium hydride (260 mg; 50% in paraffin) in toluene (10 ml). After an additional 1 h methyl iodide (1·0 g) in toluene (10 ml) was added during 45 min. The mixture was kept for 1 h at 0° and then filtered through Celite and evaporated. Distillation of the residue (45—60° at 0·02 mmHg) afforded the methyl thioformimidate (14) (794 mg, 84%), $\nu_{max.}$ ($CHCl_3$) 1733 and 1595 cm^{-1}, which was used immediately in subsequent reactions.

Hydrolysis of the Thioformimidate (14).—A solution of the thioimidate (14) (456 mg) in methanol (2·4 ml) was treated with methanolic N-hydrochloric acid (2·7 ml) (prepared by diluting concentrated hydrochloric acid with absolute methanol). After 2 days the solution was evaporated and the residue was crystallised from methanol–ether to give L-valine methyl ester hydrochloride, m.p. 167—167·5°, $[\alpha]_D^{20}$ +15·6° (*c* 2 in H_2O) (lit.,[21] +15·5°).

Benzyl N-(1-Methoxycarbonyl-2-methylpropyl)thioformimidate (15).—Thioformyl-L-valine methyl ester (13) (875 mg) was treated with sodium hydride followed by benzyl bromide (855 mg) as described for the preparation of (14). Distillation of the crude product (95—110° at 0·02 mmHg) afforded the benzyl thioformimidate (15) (1·13 g, 85%), $\nu_{max.}$ ($CHCl_3$) 1740 and 1600 cm^{-1}, which was used immediately in subsequent reactions.

1-(1-Methoxycarbonyl-2-methylpropyl)-4-methylthio-3,3-diphenylazetidin-2-one (16).—To a boiling solution of the thioimidate (14) (507 mg) in toluene (30 ml), diphenylketen (517 mg) in toluene (30 ml) was added during 2·5 h. The mixture was warmed under reflux for an additional 12 h and then evaporated. The residue was chromatographed on silica gel (preparative thick plates; 6 : 1 v/v hexane–ethyl acetate ×2) to give the β-lactam (16) (480 mg, 47%). The n.m.r. spectrum indicated the presence of a 5 : 2 mixture of two diastereoisomers. Crystallisation from ethyl acetate–hexane gave a 1·7 : 1 mixture (204 mg), m.p. 75—87°, $\nu_{max.}$ (CCl_4) 1765 and 1745sh cm^{-1}, $\delta(C_6D_6)$ 0·81 (d), 0·92 (d), 0·98 (d), and 1·09 (d) (total 6H, J 6·5 Hz, CH*Me*$_2$) 1·51 (s) and 1·81 (s) (total 3H, SMe), 2·3—3·0 (1H, m, C*H*Me$_2$), 3·18 (s) and 3·25 (s) (total 3H, OMe), 3·96 (d, J 9 Hz) and 4·15 (d, J 9·5 Hz) (total 1H, N·C*H*·CO$_2$Me),

[15] I. McMillan and R. J. Stoodley, *J. Chem. Soc.* (*C*), 1968, 2533.
[16] D. Hauser and H. P. Sigg, *Helv. Chim. Acta*, 1967, **50**, 1327.
[17] N. Maggi and G. Cignarella, *Chimica e Industria*, 1970, **52**, 164.
[18] R. B. Woodward in ' The Chemistry of Penicillin,' Princeton University Press, Princeton, New Jersey, 1949, p. 443.
[19] L. D. Cama, W. J. Leanza, T. R. Beatie, and B. G. Christensen, *J. Amer. Chem. Soc.*, 1972, **94**, 1408.
[20] R. Mayer and H. Berthold, *Z. Chem.*, 1963, **3**, 310.
[21] E. L. Smith, D. H. Spackman, and W. J. Polglase, *J. Biol. Chem.*, 1952, **199**, 801.

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5·27 (s) and 5·63 (s) (total 1H, ring H), 6·9—7·3 (Ph), and 7·4—7·8 (4H of Ph) (Found: C, 69·1; H, 6·7 N, 3·8; S, 8·2. Calc. for $C_{22}H_{25}NO_3S$: C, 68·9; H, 6·6; N, 3·65; S, 8·3%), *m/e* 383 (M^+). Evaporation of the mother liquor and crystallisation of the residue from hexane–ethyl acetate afforded the more abundant *diastereoisomer* (25 mg), m.p. 77—79°, δ(C_6D_6) 0·91 (d) and 0·98 (d) (total 6H, *J* 6·5 Hz, CH*Me*$_2$), 1·51 (3H, s, SMe), 2·3—3·0 (1H, m, CHMe$_2$), 3·25 (3H, s, OMe), 3·96 (1H, d, *J* 8·8 Hz, N·C*H*·CO$_2$Me), 5·25 (1H, s, ring H), 6·9—7·3 (Ph), and 7·5—7·8 (4H of Ph).

4-*Benzylthio*-1-(1-*methoxycarbonyl*-2-*methylpropyl*)-3,3-*diphenylazetidin*-2-*one* (17).—The thioimidate (15) (716 mg) was treated with diphenylketen (538 mg) as for the preparation of (16). Thick-plate chromatography of the crude product (6 : 1 v/v hexane–acetone × 2) gave the β-lactam (17) (854 mg, 69%) as a 3 : 1 mixture of two diastereoisomers (n.m.r.), m.p. 44—60° (from ethyl acetate–hexane), ν$_{max.}$ ($CHCl_3$) 1770 and 1740 cm^{-1}, δ(C_6D_6), 3·15 (s) and 3·29 (s) (total 3H, OMe), and 5·41 (s) and 5·78 (s) (total 1H, ring H) (Found: C, 73·4; H, 6·55; N, 3·1; S, 6·9. Calc. for $C_{28}H_{29}NO_3S$: C, 73·2; H, 6·4; N, 3·05; S, 7·0%), *m/e* 459 (M^+). An additional chromatography on Florisil with 2 : 1 v/v hexane–methylene dichloride as eluant yielded in the last eluted fraction the more abundant *diastereoisomer*, δ(C_6D_6) 0·93 (d) and 0·95 (d) (total 6H, *J* 6·5 Hz, CH*Me*$_2$), 2·3—2·9 (1H, m, C*H*Me$_2$), 3·28 (3H, s, OMe), 3·46 and 3·56 (2H, inner lines of an AB quartet, C*H*$_2$Ph), 3·92 (1H, d, *J* 9·5 Hz, N·C*H*·CO$_2$Me), 5·34 (1H, s, ring H), and 6·9—7·5 (Ph).

1-(1-*Methoxycarbonyl*-2-*methylpropyl*)-4-*methylthio*-3-*phthalimidoazetidin*-2-*one* (18).—To a stirred solution of freshly prepared thioimidate (14) (473 mg) and triethylamine (253 mg) in toluene (25 ml), phthaloylglycyl chloride (560 mg) in toluene (25 ml), was added during 2 h. The precipitated triethylammonium chloride was filtered off and the filtrate was evaporated. The residue was chromatographed on silica gel (thick plates; 5 : 2 v/v hexane–acetone × 2) to give the β-lactam (18) (376 mg, 40%) as a 1 : 1 mixture of two diastereoisomers (n.m.r.), m.p. 133—145° (from hexane–ethyl acetate), ν$_{max.}$ (KBr) 1785, 1767, 1745, 1730sh, and 1725br cm^{-1}, δ(C_6D_6) 0·99 (d), 1·02 (d), 1·16 (d), and 1·27 (d) (total 6H, *J* 7 Hz, CH*Me*$_2$), 1·76 (s), and 1·88 (s) (total 3H, SMe), 2·3—3·2 (1H, m, C*H*Me$_2$), 3·48 (s) and 3·59 (s) (total 3H, OMe), 3·92 (d, *J* 9 Hz) and 3·99 (d, *J* 8 Hz) (total 1H, N·C*H*·CO$_2$Me), 5·10 (d) and 5·15 (d) (total 1H, *J* 2·6 Hz, ring H), 5·44 (d) and 5·47 (d) (total 1H, *J* 2·6 Hz, ring H), and 6·9—7·5 (aromatic) (Found: C, 57·4; H, 5·1; N, 7·5; S, 8·5. Calc. for $C_{18}H_{20}N_2O_5S$: C, 57·4; H, 5·35; N, 7·4; S, 8·5%), *m/e* 376 (M^+).

4-*Benzylthio*-1-(1-*methoxycarbonyl*-2-*methylpropyl*)-3-*phthalimidoazetidin*-2-*one* (19).—To a stirred solution of freshly prepared thioimidate (15) (667 mg) and triethylamine (253 mg) in toluene (25 ml), phthaloylglycyl chloride (561 mg) in toluene (25 ml) was added during 5 h. The precipitated triethylammonium chloride was filtered off and the filtrate was evaporated. The residue was chromatographed on a silica gel column [17 : 2 : 1 (v/v) methylene dichloride–hexane–chloroform as eluant] to give the β-lactam (19) (442 mg, 39%) as a 1 : 1 mixture of two diastereoisomers (n.m.r.), m.p. 88—89° (from hexane–ethyl acetate), ν$_{max.}$ (KBr) 1783sh, 1770, 1740sh, and 1720 cm^{-1}, δ(C_6D_6) 0·94 (d), 1·03 (d), 1·15 (d), and 1·22 (d) (total 6H, *J* 7 Hz, CHMe$_2$), 2·5—3·1 (1H, m, C*H*Me$_2$), 3·50 (s) and 3·59 (s) (total 3H, OMe), 3·55 (s, A$_2$ pattern, S·C*H*$_2$Ph) 3·70 and 3·73 (inner lines of an AB pattern, S·C*H*$_2$Ph) (total 2H), 3·93 (d) and 4·08 (d) (total 1H, *J* 9 Hz, N·C*H*·CO$_2$Me), 5·17 (d) and 5·23 (d) (total 1H, *J* 2·6 Hz, ring H), 5·39 (d) and 5·41 (d) (total 1H, *J* 2·6 Hz, ring H), and 6·8—7·5 (aromatic) (Found: C, 63·8; H, 5·5; N, 6·3; S, 7·2. Calc. for $C_{24}H_{24}N_2O_5S$: C, 63·7; H, 5·35; N, 6·2; S, 7·1%), *m/e* 452 (M^+).

4-*Benzylthio*-3-*chloro*-1-(1-*methoxycarbonyl*-2-*methylpropyl*)-*azetidin*-2-*one* (20).—To a stirred solution of freshly distilled thioimidate (15) (2·65 g) and triethylamine (2·10 g) in toluene (50 ml), chloroacetyl chloride (2·27 g) in toluene (100 ml) was added during 2·5 h. The mixture was filtered and evaporated. Column chromatography of the residue over acid-washed alumina [15 : 1 v/v benzene–ethyl acetate as eluant] afforded the chloro-β-lactam (20) (1·54 g, 45%) as a 5 : 3 mixture of two diastereoisomers (n.m.r.). The isomeric β-lactams were separated by repeated chromatography on Florisil [1 : 1 v/v hexane–methylene dichloride as eluant] to give first the more abundant *isomer*, m.p. 52—53° (from hexane–ethyl acetate), [α]$_D^{20}$ −65° (*c* 1 in $CHCl_3$), ν$_{max.}$ ($CHCl_3$) 1775 and 1742 cm^{-1}, δ(C_6D_6) 0·87 (d) and 0·93 (d) (total 6H, *J* 7 Hz, CH*Me*), 2·1—2·9 (1H, m, C*H*Me$_2$), 3·35 (3H, s, OMe), 3·47 (2H, s, C*H*$_2$Ph), 3·65 (1H, d, *J* 8 Hz, N·CH·CO$_2$Me), 4·38 (1H, d, *J* 1·9 Hz, ring H), 4·55 (1H, d, *J* 1·9 Hz, ring H), and 7·0—7·3 (Ph) (Found: C, 56·2; H, 5·9; Cl, 10·6; N, 4·0; S, 10·1. $C_{16}H_{20}ClNO_3S$ requires C, 56·2; H, 5·9; Cl, 10·4; N, 4·1; S, 9·4%), *m/e* 341 (M^+), and then the second *isomer*, an oil (t.l.c. pure), ν$_{max.}$ ($CHCl_3$), 1780 and 1742 cm^{-1}, δ(C_6D_6) 0·74 (d) and 0·96 (d) (total 6H, *J* 6·5 Hz, CH*Me*$_2$), 2·1—2·8 (1H, m, C*H*Me$_2$), 3·26 (3H, s, OMe), 3·53 and 3·54 (2H, inner lines of an AB pattern, S·C*H*$_2$Ph), 3·74 (1H, d, *J* 9 Hz, N·C*H*·CO$_2$Me), 4·33 (1H, d, *J* 1·7 Hz, ring H), 4·68 (1H, d, *J* 1·7 Hz, ring H), and 6·9—7·3 (Ph).

3-*Azido*-4-*benzylthio*-1-(1-*methoxycarbonyl*-2-*methylpropyl*)-*azetidin*-2-*one* (21).—(*a*) A solution of compound (20) (3·26 g) (the isomer of m.p. 52—53° or a 5 : 3 mixture of the two diastereoisomers) and sodium azide (1·25 g) in dimethyl sulphoxide (25 ml) was stirred at 70° during 24 h and then cooled. A mixture of water and ether was added and the aqueous layer was extracted with ether. The combined extracts were washed with water, dried, and evaporated. The residue was chromatographed over Florisil [elution with hexane–methylene dichloride of varying composition (starting from 3 : 1 v/v)] to give first a 1 : 1 mixture of the two diastereoisomers (20) (1·76 g, 54%) (the isomeric ratio of the recovered starting material was independent of the initial isomeric ratio), and then the azido-β-lactam (21) (824 mg, 25%). The first-eluted portion of (21) consisted of one pure *isomer*, m.p. 52—54° (from hexane–ethyl acetate), ν$_{max.}$ ($CHCl_3$) 2122, 1770, and 1738 cm^{-1}, δ(C_6D_6) 0·76 (d) and 1·00 (d) (total 6H, *J* 6·5 Hz, CH*Me*$_2$), 2·2—2·7 (1H, m, C*H*Me$_2$), 3·30 (3H, s, OMe), 3·70 and 3·74 (2H, inner lines of an AB quartet, S·C*H*$_2$Ph) 4·00 (d, *J* 9·5 Hz, N·C*H*·CO$_2$Me) and 3·96 (d, *J* 4·7 Hz, ring H) (2H), 4·81 (1H, d, *J* 4·7 Hz, ring H), and 7·0—7·3 (Ph) (Found: C, 55·4; H, 5·8; N, 16·2; S, 9·3. $C_{16}H_{20}N_4O_3S$ requires C, 55·2; H, 5·8; N, 16·1; S, 9·2%). After a middle fraction containing a mixture of the two isomers, the second *isomer* was eluted, m.p. 76—77° (from hexane–ethyl acetate), ν$_{max.}$ ($CHCl_3$) 2125, 1775, and 1740 cm^{-1}, δ(C_6D_6) 0·85 (d) and 0·90 (d) (total 6H, *J* 6·5 Hz, CH*Me*$_2$), 2·2—2·8 (1H, m, C*H*Me$_2$), 3·29 (3H, s, OMe), 3·48 (1H, d, *J* 8·5 Hz, N·C*H*·CO$_2$Me), 3·49 (2H, s, S·C*H*$_2$Ph),

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3·98 (1H, d *J* 5 Hz, ring H), 4·40 (1H, d, *J* 5 Hz, ring H), and 7·0—7·25 (Ph) (Found: C, 55·1; H, 5·6; N, 16·2; S, 9·2%), *m/e* 348 (very weak, M^+) and 320 ($M^+ - 28$). The n.m.r. spectra of the various fractions indicated that the two isomers of (21) were obtained in equal amounts.

(*b*) The lactam (20) (342 mg; a 5 : 3 isomeric mixture) and sodium azide (72 mg) in dimethylformamide (5 ml) were stirred at 110° during 48 h and then cooled. The mixture was worked up as in (*a*) and the residue was chromatographed on silica gel thick plates (15 : 1 v/v benzene–ethyl acetate) to yield unchanged (20) (100 mg, 29%) and (21) (40 mg, 11%); t.l.c. and spectral data as in (*a*).

3-*Amino*-4-*benzylthio*-1-(1-*methoxycarbonyl*-2-*methylpropyl*)*azetidin*-2-*one* (22).—(*a*) To a stirred solution of compound (21) (m.p. 52—54°; 270 mg) in 90% acetic acid (3 ml), zinc dust (270 mg) was added during 20 min. The mixture was filtered through a short column of silica gel, and evaporated. The residue was treated with triethylamine (800 mg) in ether (10 ml). The precipitate was filtered off and the filtrate was evaporated to give the cis-*amino*-β-*lactam* (22) (200 mg, 80%), $\nu_{max.}$ (CCl_4) 3390vw, 1777, and 1743 cm^{-1}, δ(C_6D_6) 0·83 (d) and 1·05 (d) (total 6H, *J* 6·5 Hz, CH*Me*$_2$), 1·33br (2H, disappears on addition of D_2O, NH_2), 2·2—2·9 (1H, m, C*H*Me$_2$), 3·31 (3H, s, OMe), 3·65br (2H, s, S·C*H*$_2$Ph), 3·91 (1H, d, *J* 4·7 Hz, ring H), 4·16 (1H, d, *J* 9·5 Hz, N·C*H*·CO_2Me), 4·87 (1H, d, *J* 4·7, ring H), and 7·0—7·3 (Ph), *m/e* 322 (M^+). Toluene-*p*-sulphonic acid monohydrate (130 mg) was added to a solution of compound (22) (200 mg) in ether–ethyl acetate (2 : 1 v/v, 1·5 ml). The mixture became clear within a few s and solidified after 15 min. Trituration with ether and crystallisation from ethyl acetate–ether gave the *toluene*-p-*sulphonate*, m.p. 137—138·5°, $\nu_{max.}$ (KBr) 2400—3200, 1776, 1744, 1603, and 1545 cm^{-1} (Found: C, 56·05; H, 6·05; N, 5·8; S, 12·7. $C_{23}H_{30}N_2O_6S_2$ requires C, 55·9; H, 6·1; N, 5·7; S, 12·9%).

(*b*) Reduction of the diastereoisomer (21) of m.p. 76—77° as described in (*a*) gave the corresponding cis-*amino*-β-*lactam* (22), $\nu_{max.}$ (CCl_4) 1770 and 1743 cm^{-1}, δ(C_6D_6) 0·89 (d) and 0·94 (d) (total 6H, *J* 7 Hz, CH*Me*$_2$), 2·53 (2H, s, disappears on addition of D_2O, NH_2), 2·1—2·3 (1H, m, C*H*Me$_2$), 3·35 (3H, s, OMe), 3·50 (2H, s, S·C*H*$_2$Ph), 3·77 (1H, d, *J* 8 Hz, N·C*H*·CO_2Me), 4·01 (1H, d, *J* 4·8 Hz, ring H), 4·56 (1H, d, *J* 4·8 Hz, ring H) and 7·0—7·3 (Ph); *toluene*-p-*sulphonate*, m.p. 170—171°, $\nu_{max.}$ (KBr) 2300—3200, 1786, 1735, 1598, and 1532 cm^{-1} (Found: C, 55·8; H, 5·9; N, 5·8; S, 12·75%).

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