Studies Related to Penicillins and Cephalosporins. Part IV.[1] Synthesis of Methyl 7-Phthalimido-6,7-*trans*-DL-cepham-4-carboxylate

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β-Lactams having a common nitrogen atom with methionine methyl ester were prepared. 1-(1-Methoxycarbonyl-3-methylthiopropyl)-3-phthalimido-4-triphenylmethylthioazetidin-2-one (16) was obtained by the reaction of triphenylmethyl *N*-(1-methoxycarbonyl-3-methylthiopropyl)thioformimidate (11) with phthaloylglycyl chloride and triethylamine. Detritylation of (16) afforded the corresponding mercapto-β-lactam (15). Treatment of (16) with methyl iodide and sodium iodide in dimethylformamide gave 1-(3-iodo-1-methoxycarbonylpropyl)-3-phthalimido-4-triphenylmethylthioazetidin-2-one (18). This compound was converted into a mercuriothio-derivative (19) which gave methyl 7-phthalimido-6,7-*trans*-DL-cepham-4-carboxylate (20) by an intramolecular alkylation on the sulphur atom.

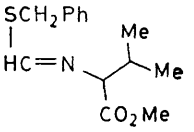
A SCHEME for the use of natural and synthetic α-amino-carboxylic acids as starting materials for the preparation of penicillin and cephalosporin nuclear analogues has been outlined.[2] The conversion of L-valine methyl ester through its benzyl thioformimidate derivative (1) into the β-lactams (2)—(5) was described and it was suggested[2] that other α-amino-acids could be converted in a similar way into β-lactams of type (6), where X represents an amino- or a potential amino-group, R^2 the α-amino-acid side chain, and R^1 and R^3 sulphur- and oxygen-protecting groups, respectively. It was postulated[2] that, provided the sulphur-protecting group R^1 is suitably chosen and that the side chain R^2 contains a functional group allowing ring closure on to the sulphur atom, compounds (6) might serve as intermediates in a general method for the synthesis of bicyclic β-lactams, structurally related to penicillins and cephalosporins. The feasibility of this method has now been substantiated by the synthesis of the bicyclic β-lactam (20), a simple analogue of cephalosporin C (7).

When this work was in progress,[3] little was known about the preparation and properties of 4-mercapto-β-lactams.[4] These compounds were considered rather unstable, requiring the use of a protecting group R^1 which could be removed under mild conditions. A report[5] claiming that the *S*-*p*-nitrobenzyl group can be removed from *S*-*p*-nitrobenzyl-L-cysteine by catalytic hydrogenation prompted us to choose this group for sulphur protection. However, it was subsequently found that catalytic hydrogenation gives the *p*-aminobenzyl derivative; sulphur deblocking required an additional treatment with a mercury salt followed by hydrogen sulphide.[6]

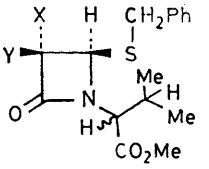
The β-lactam (12) was chosen as the first synthetic target. Treatment of *N*-thioformyl-DL-methionine methyl ester (8) with sodium hydride in toluene, followed by alkylation with *p*-nitrobenzyl chloride, gave

[1] Part III, M. D. Bachi and O. Goldberg, *J.C.S. Perkin I*, 1974, 1184.
[2] M. D. Bachi and O. Goldberg, *J.C.S. Chem. Comm.*, 1972, 319; *J.C.S. Perkin I*, 1972, 2332.
[3] Preliminary report, M. D. Bachi and K. J. Ross-Petersen, *J.C.S. Chem. Comm.*, 1974, 12.
[4] J. C. Sheehan, U.S.P. 3,487,074/1969.
[5] C. Berse, R. Boucher, and L. Piché, *J. Org. Chem.*, 1957, **22**, 805.
[6] M. D. Bachi and K. J. Ross-Petersen, *J. Org. Chem.*, 1972, **37**, 3550.

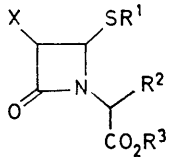
the thioformimidate (9), which was converted into the β-lactam (12) with phthaloylglycyl chloride and triethylamine [22%, based on (8)]. N.m.r. spectroscopy revealed the presence of a 1 : 1 mixture of two *trans*-diastereoisomers, subsequently separated by crystallisation from



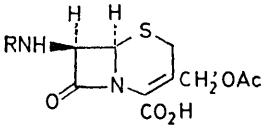
(1)



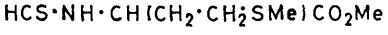
(2) X = phthalimido, Y = H
(3) X = Cl, Y = H
(4) X = H, Y = N_3
(5) X = H, Y = NH_2



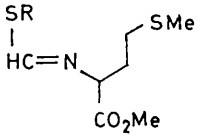
(6)



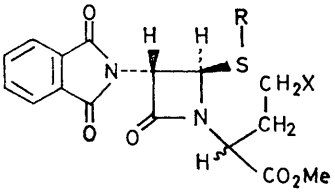
(7) R = D-5-amino-5-carboxyvaleryl



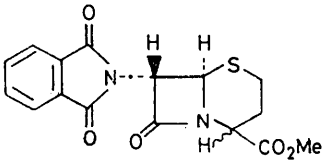
(8)



(9) R = *p*-$NO_2 \cdot C_6H_4 \cdot CH_2$
(10) R = Me
(11) R = Ph_3C



(12) R = *p*-$NO_2 \cdot C_6H_4 \cdot CH_2$, X = SMe
(13) R = *p*-$NO_2 \cdot C_6H_4 \cdot CH_2$, X = $SMe_2^+I^-$
(14) R = *p*-$NH_2 \cdot C_6H_4 \cdot CH_2$, X = SMe
(15) R = H, X = SMe
(16) R = Ph_3C, X = SMe
(17) R = Ph_3C, X = $SMe_2^+I^-$
(18) R = Ph_3C, X = I
(19) R = Hg —, X = I



(20)

carbon tetrachloride. One isomer, m.p. 139—140°, displays for the ring protons the AB pattern: δ (C_6D_6) 5.00 (d) and 5.20 (d) (*J* 2.8 Hz) and the other isomer (oil) shows δ (C_6D_6) 5.08 (d) and 5.29 (d) (*J* 2.5 Hz). These isomers were converted into their sulphonium salts (13) (79—88%) with methyl iodide.

Attempts to remove the *S*-*p*-nitrobenzyl group in the β-lactams (13) by catalytic hydrogenation were unsuccessful. Hydrogenation of each of the two isomeric β-lactams (12) over 10% palladium–charcoal in acidic methanol resulted only in reduction of the nitro-group to give the *S*-*p*-aminobenzyl β-lactams (14). These lactams were also obtained (57%) by hydrogenation in dioxan–acetic acid. The 4-mercapto-β-lactams (15) were eventually obtained (60%) by treatment of the *p*-aminobenzyl derivatives (14) with mercury(II) salts followed by hydrogen sulphide.

We also considered the use of other sulphur-protecting groups which can be split off by heavy metal salts with-

out need for preliminary hydrogenation.* The trityl group is frequently used in peptide synthesis for this purpose,[7] and its use for the protection of various 4-mercapto-β-lactams has been recently reported.[8]

Difficulties were encountered in direct *S*-tritylation of the thioamide (8) with trityl chloride. The thioimidate (11) was therefore prepared by warming the methyl thioimidate (10) with triphenylmethanethiol under reduced pressure. Treatment of compound (11) with phthaloylglycyl chloride and triethylamine gave the β-lactam (16) (74%). The n.m.r. spectrum indicated the presence of a *ca.* 1 : 1 mixture of two *trans*-diastereoisomers, subsequently separated by column chromatography over Florisil. The n.m.r. spectrum of the first-eluted isomer, m.p. 174—175°, displays for the ring protons the AB pattern: δ (C_6D_6) 5.17 (d) and 5.70 (d) (*J* 2.5 Hz) and that of the second, m.p. 142—143°, shows δ (C_6D_6) 5.20 (d) and 5.67 (d) (*J* 2.5 Hz). Detritylation of the two isomeric β-lactams (16) with mercury(II) chloride in methanol at 40—50 °C afforded the corresponding mercuriothio-derivatives, which were converted into the free thiols (15) (29%) by treatment with hydrogen sulphide. The n.m.r. spectra of the two diastereoisomeric β-lactams (15) exhibit doublets for the thiol protons which disappear on treatment with D_2O. The ring protons of one isomer give rise to the pattern: δ (C_6D_6) 4.85 (dd) (*J* 2.5 and 9.0 Hz) and 5.19 (d) (*J* 2.5 Hz), and those of the other to δ (C_6D_6) 4.99 (dd) (*J* 2.5 and 10 Hz) and 5.29 (d) (*J* 2.5 Hz). The mercapto-β-lactams could be readily reconverted into the corresponding 4-tritylthio-β-lactams (16) by treatment with trityl chloride in chloroform. The mercapto-β-lactam obtained by deblocking the oily isomer of the *S*-*p*-nitrobenzylthio-β-lactam (12) was identical with that obtained by detritylation of the less polar isomer of the β-lactam (16) (m.p. 174—175°), and the mercapto-β-lactam obtained by deprotection of the crystalline isomer of the *S*-*p*-nitrobenzylthio-β-lactam (12) was identical with that obtained by detritylation of the more polar isomer of the β-lactam (16) (m.p. 142—143°).

Attempts have been made to activate the side chain of the methionine system by converting the β-lactam (16) into its sulphonium salt (17). However, alkylation under the mild conditions successfully employed for the preparation of the sulphonium salts (13) resulted in a poor yield. The formation of a sulphonium salt from an alkyl halide and a sulphide is reversible,[9] and it seems that the bulky trityl group contributes to the displacement of the equilibrium from (17) to (16). Therefore the sulphonium salt (17) was not isolated but was converted *in situ* into the iodo-β-lactam (18). Thus, when the β-lactam (16) (m.p. 142—143°) was warmed with an excess of methyl iodide and sodium iodide in dimethylformamide, the iodo-β-lactam (18) was obtained (50%). Treatment of the β-lactam (18) with mercury(II) chloride in methanol afforded a mercury compound (19). This was warmed in dimethylformamide to give, by intramolecular alkylation, methyl 7-phthalimido-6,7-*trans*-DL-cepham-4-carboxylate (20) (59%).

An attempt[10] to prepare the cepham system by the route used for the total synthesis of penicillin[11] has been reported to afford a complex mixture which contained only traces of the desired bicyclic β-lactam.

EXPERIMENTAL

M.p.s were determined with a Büchi apparatus. I.r. spectra were taken on a Perkin-Elmer 237 grating spectrometer. ^1H N.m.r. data were usually recorded on a Varian A60 spectrometer; the 90 MHz spectra were recorded on a Brucker HFX90 spectrometer. Mass spectra were recorded on an Atlas MAT CH4 instrument. Compounds (8)—(12), (16), and (20) were prepared under nitrogen in dry solvents.

N-*Thioformyl*-DL-*methionine Methyl Ester* (8) (with E. LALLOUZ).—A solution of DL-methionine methyl ester hydrochloride (10.0 g), triethylamine (5.1 g), and *O*-ethyl thioformate[12] (9.0 g) in methanol (60 ml) was left for 20 h at room temperature and then evaporated. The residue was treated with ether, the precipitated triethylammonium chloride was filtered off, and the filtrate was evaporated. The residue was dissolved in chloroform and filtered through a short silica gel column to give, after distillation (140—145° at 0.05 mmHg), the *thioformyl ester* (8) (8.0 g, 78%), δ ($CDCl_3$) 2.11 (3 H, s, SMe), 2.48 (4 H, m, CH·CH_2·CH_2·S), 3.85 (3 H, s, OMe), 5.43 (1 H, m, N·CH·CO_2Me), 8.93br (1 H, NH), and 9.58 (1 H, d, *J* 6 Hz, HCS) (Found: C, 40.75; H, 6.4; N, 6.7; S, 30.7. $C_7H_{13}NO_2S_2$ requires C, 40.6; H, 6.3; N, 6.8; S, 30.9%), *m/e* 207 (M^+).

1-(1-*Methoxycarbonyl*-3-*methylthiopropyl*)-4-(p-*nitrobenzylthio*)-3-*phthalimidoazetidin*-2-*one* (12).—A solution of the thioamide (8) (2.07 g) in toluene (75 ml) was added at room temperature to a stirred suspension of sodium hydride (0.60 g; 50% in paraffin) in toluene (75 ml). After 30 min a solution of *p*-nitrobenzyl chloride (2.57 g) in toluene (40 ml) was added at once, and the black mixture was vigorously stirred for an additional 90 min and then filtered through Celite, which retained most of the coloured material. The Celite was washed with toluene (100 ml) and the filtrates, containing the thioformimidate (9), were combined. To this, and triethylamine (3.03 g), a solution of phthaloylglycyl chloride[13] (4.67) in toluene (150 ml) was added during 6 h with vigorous stirring. The mixture was stirred for an additional 20 h, filtered through Celite, and evaporated. Column chromatography of the residue over silica gel (Merck GF_{254}; 9 : 1 v/v chloroform–ethyl acetate as eluant) gave the β-lactam (12) (1.14 g, 22%) as a 1 : 1 mixture of two diastereoisomers (n.m.r.). Crystallisation from carbon tetrachloride (40 ml) afforded a *crystalline isomer*, m.p. 139—140°;

* See ref. 1 for the use of the *p*-methoxybenzyl group for sulphur protection in a 4-mercapto-β-lactam.

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[8] R. Lattrell, *Annalen*, 1974, 1961.

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[10] J. C. Sheehan and J. A. Schneider, *J. Org. Chem.*, 1966, **31**, 1635.

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[12] R. Mayer and H. Berthold, *Z. Chem.*, 1963, **3**, 310.

[13] J. C. Sheehan and V. S. Frank, *J. Amer. Chem. Soc.*, 1949, **71**, 1856.

$\nu_{max.}$ (KBr) 1 786, 1 779, 1 754, and 1 724 cm^{-1}, δ (C_6D_6–$CDCl_3$) * 1.98 (3 H, s, SMe), 2.1—2.85 (4 H, m, CH·CH_2·CH_2·S), 3.55 (2 H, s, CH_2Ar), 3.62 (3 H, s, OMe), 4.52 (1 H, t, *J* 7 Hz, N·C*H*·CO_2Me), 5.00 (1 H, d, *J* 2.8 Hz, ring H), 5.20 (1 H, d, *J* 2.8 Hz, ring H), and 6.7—7.9 (complex aromatic) (Found: C, 54.5; H, 4.3; N, 8.1; S, 12.3. $C_{24}H_{23}N_3O_7S_2$ requires C, 54.4; H, 4.4; N, 7.9; S, 12.2%), *m/e* 529 (M^+); and a second *non-crystalline isomer* (t.l.c. pure) $\nu_{max.}$ ($CHCl_3$), 1 786sh, 1 776, 1 739sh, and 1 725 cm^{-1}, δ (C_6D_6) 1.87 (3 H, s, SMe), 2.2—3.0 (4 H, m, CH·CH_2·CH_2·S), 3.40 (3 H, s, OMe), 3.47 (2 H, s, CH_2Ar), 4.6 (1 H, m, N·C*H*·CO_2Me), 5.08 (1 H, d, *J* 2.5 Hz, ring H), 5.29 (1 H, d, *J* 2.5 Hz, ring H), and 6.7—7.8 (complex, aromatic) *m/e* 529 (M^+).

1-(3-*Dimethylsulphonio*-1-*methoxycarbonylpropyl*)-4-(p-*nitrobenzylthio*)-3-*phthalimidoazetidin*-2-*one Iodide* (13).—(*a*) A mixture of the crystalline isomer of (12) (225 mg) and methyl iodide (10 ml) in acetone (10 ml) was kept at room temperature for 3 days. The precipitated product was filtered off to give one *isomer* of the β-lactam (13) (250 mg, 88%), m.p. 131—132° (decomp.) (from methanol), $\nu_{max.}$ (KBr) 1 786 sh, 1 773, 1 739, and 1 718 cm^{-1} (Found: C, 44.5; H, 3.9; N, 6.15; S, 9.5. $C_{25}H_{26}IN_3O_7S_2$ requires C, 44.7; H, 3.9; N, 6.3; S, 9.55%).

(*b*) A solution of the non-crystalline isomer of (12) (200 mg) in methyl iodide (5 ml) was kept at room temperature for 24 h. The precipitated product was filtered off to give another *isomer* of the β-lactam (13) (200 mg, 79%), m.p. 110—115° (decomp.). Recrystallisation from methanol afforded a sample of m.p. 125—126° (decomp.), $\nu_{max.}$ (KBr) 1 786sh, 1 773, 1 754, and 1 724 cm^{-1} (Found: C, 44.8; H, 3.9; N, 6.2; S, 9.4%).

4-(p-*Aminobenzylthio*)-1-(1-*methoxycarbonyl*-3-*methylthiopropyl*)-3-*phthalimidoazetidin*-2-*one* (14).—(*a*) A solution of the non-crystalline isomer of (12) (260 mg) in dioxan (4 ml) and acetic acid (0.5 ml) was hydrogenated at room temperature and atmospheric pressure over 10% palladium–charcoal (260 mg). After 4 h the catalyst was filtered off and the filtrate evaporated. The residue, which gave a negative nitroprusside test for thiols, was chromatographed on silica gel (preparative thick plates; 4 : 1 v/v chloroform–ethyl acetate as eluant) to give an isomer of the β-lactam (14) (140 mg, 57%), an oil, $\nu_{max.}$ ($CHCl_3$) 1 786, 1 773, 1 745, and 1 727 cm^{-1}, δ ($CDCl_3$) 2.15 (3 H, s, SMe), 2.0—3.0 (4 H, m, CH·CH_2·CH_2·S), 3.26br (2 H, NH_2, disappears on treatment with D_2O), 3.84br (5 H, OMe and CH_2Ar), 4.42 (1 H, m, *N*·C*H*·CO_2Me), 5.19 (1 H, d, *J* 2.5 Hz, ring H), 5.28 (1 H, d, *J* 2.5 Hz, ring H), 6.45 (2 H, d, *J* 9 Hz, aromatic), 7.05 (2 h, d, *J* 9 Hz, aromatic), and 7.82 (4 H, m, aromatic), *m/e* 499 (M^+).

(*b*) Hydrogenation of the crystalline (m.p. 139—140°) isomer of (12) under the conditions described in (*a*) afforded an isomer of the β-lactam (14), in oil, δ ($CDCl_3$) (90 MHz) 2.15 (3 H, s, SMe), 2.05—3.3 (6 H, m, CH·CH_2·CH_2·S and NH_2), 3.75 (2 H, s, CH_2Ar), 3.85 (3H, s, OMe), 4.45 (1 H, m, N·C*H*·CO_2Me), 5.10 (1 H, d, *J* 2.0 Hz, ring H), 5.23 (1 H, d, *J* 2.0 Hz, ring H), 6.40 (2 H, d, *J* 8.5 Hz, aromatic), 7.15 (2 H, d, *J* 8.5 Hz, aromatic), and 7.83 (4 H, m, aromatic).

Methyl N-(1-*Methoxycarbonyl*-3-*methylthiopropyl*)*thioformimidate* (10) (with E. Lallouz).—A solution of the thioamide (8) (520 mg) in toluene (10 ml) was added at room temperature to a suspension of sodium hydride (84 mg) in toluene (2.5 ml). After 30 min methyl iodide (710 mg) in toluene (5 ml) was added. The mixture was stirred for an additional 1 h and then filtered through Celite and evaporated. Distillation of the residue (100—110° at 0.5 mmHg) afforded the methyl thioformimidate (10) (484 mg, 88%), $\nu_{max.}$ (film) 1 739 and 1 600 cm^{-1}, which was used immediately in the subsequent reaction.

Trityl N-(1-*Methoxycarbonyl*-3-*methylthiopropyl*)*thioformimidate* (11).—A stirred mixture of equimolecular amounts of the thioimidate (10) and triphenylmethanethiol [14] was kept at 50—55° under reduced pressure (10 mmHg) during 45 h to give the trityl thioimidate (11) (crude, quantitative), $\nu_{max.}$ ($CHCl_3$) 1 742 and 1 597 cm^{-1}, which was used immediately in the subsequent reaction.

1-(1-*Methoxycarbonyl*-3-*methylthiopropyl*)-3-*phthalimido*-4-*tritylthioazetidin*-2-*one* (16).—To a stirred solution of the freshly prepared thioimidate (11) (0.50 g) and triethylamine (0.44 g) in toluene (50 ml), phthaloylglycyl chloride (0.80 g) in toluene (75 ml) was added during 8 h. The precipitated triethylammonium chloride was filtered off and the filtrate was chromatographed on a silica gel column (Merck GF_{254}; 2 : 1 v/v hexane–acetone) to give the β-lactam (16) (0.56 g, 79%) as a 1 : 1 mixture of two diastereoisomers (n.m.r.). The isomeric β-lactams were separated by chromatography on Florisil (elution with hexane–methylene chloride of varying composition, starting from 2 : 1 v/v) to give one *isomer*, m.p. 174—175° (from methanol), $\nu_{max.}$ (KBr) 1 783, 1 770, 1 739, and 1 720 cm^{-1}, δ (C_6D_6) 1.95 (3 H, s, SMe), 2.1—3.0 (4 H, m, CH·CH_2·CH_2·S), 3.42 (3 H, s, OMe), 4.0 (1 H, m, N·C*H*·CO_2Me), 5.17 (1 H, d, *J* 2.5 Hz, ring H), 5.70 (1 H, d, *J* 2.5 Hz, ring H), and 6.7—7.8 (complex, aromatic) (Found: C, 68.0; H, 4.9; N, 4.2; S, 10.4. $C_{36}H_{32}N_2O_5S_2$ requires C, 67.9; H, 5.1; N, 4.4; S, 10.05%), and then the *second isomer*, m.p. 142—143° (from methanol), $\nu_{max.}$ (KBr) 1 783, 1 773, 1 742, and 1 721 cm^{-1}, δ (C_6D_6) 1.85 (3 H, s, SMe), 2.1—2.8 (4 H, m, CH·CH_2·CH_2·S), 3.57 (3 H, s, OMe), 4.45 (1 H, m, N·C*H*·CO_2Me), 5.20 (1 H, d, *J* 2.5 Hz, ring H), 5.67 (1 H, d, *J* 2.5 Hz, ring H), and 6.7—7.6 (complex, aromatic) (Found: C, 67.9; H, 5.1; N, 4.35; S, 10.1%).

Preparation and Tritylation of 4-*Mercapto*-1-(1-*methoxycarbonyl*-3-*methylthiopropyl*)-3-*phthalimidoazetidin*-2-*one* (15).—(*a*) A mixture of the more polar isomer of (16), m.p. 142—143° (175 mg), and mercury(II) chloride (150 mg) in methanol (3 ml) was stirred at 40 °C for 3 h. The resulting white precipitate was filtered off and washed with methanol (5 ml) and ether (5 ml) to give a mercury salt (140 mg), m.p. 192—193° (decomp.). A suspension of this compound (136 mg) in methanol (5 ml) was saturated with hydrogen sulphide. After 90 min the mercury sulphide was filtered off and the filtrate was evaporated to give an isomer of the mercapto-β-lactam (15) (29 mg, 28%), $\nu_{max.}$ ($CHCl_3$) 1 783sh, 1 773, 1 740sh, and 1 724 cm^{-1}, δ (C_6D_6) (90 MHz) 1.82 (1 H d, *J*, 9 Hz, SH), 1.88 (3 H, s, SMe), 2.2—2.8 (4 H, m, CH·CH_2·CH_2·S), 3.43 (3 H, s, OMe), 4.54 (1 H, t, *J* 7 Hz, N·C*H*·CO_2Me), 4.85 (1 H, dd, *J* 2.5 and 9 Hz, ring 4-H), 5.19 (1 H, d, *J* 2.5 Hz, ring 3-H) (after treatment with D_2O: δ 1.82 absent, δ 4.85 becomes d, *J* 2.5 Hz).

This mercapto-β-lactam (20 mg) was stirred with trityl chloride (28 mg) in chloroform (1 ml) for 30 min and the mixture was then evaporated. The residue was chromatographed on silica gel (Merck GF_{254} thick plates; 2 : 1 v/v hexane–acetone as eluant) to give the more polar isomer of (16) (15 mg), m.p. and mixed m.p. 142—143°.

(*b*) A mixture of the less polar isomer of (16), m.p. 174—175° (160 mg) was treated with mercury(II) chloride as

* A few drops of $CDCl_3$ were added to assist dissolution of the sample in C_6D_6.

[14] N. Kharasch and H. R. Williams, *J. Amer. Chem. Soc.*, 1950, **72**, 1843.

described in (*a*) to give a mercury salt (155 mg), m.p. 158—159° (decomp.). This compound (148 mg) was treated with hydrogen sulphide, to give, after work-up as described in (*a*), an isomer of the mercapto-β-lactam (15) (29 mg, 30%), $\nu_{max.}$ ($CHCl_3$) 1 790sh, 1 779, 1 735sh, and 1 730 cm^{-1}, δ (C_6D_6) (90 MHz) 1.89 (3 H, s, SMe), 2.00 (1 H, d, *J* 10 Hz, SH), 2.6—3.0 (4 H, m, CH·C*H*$_2$·C*H*$_2$·S), 3.40 (3 H, s, OMe), 4.5 (1 H, m, N·C*H*·CO_2Me), 4.99 (1 H, dd, *J* 2.5 and 10 Hz, ring 4-H), 5.29 (1 H, d, *J* 2.5 Hz, ring 3-H), and 6.8—7.6 (m, aromatic) (after treatment with D_2O: δ 2.00 absent, δ 4.99 becomes d, *J* 2.5 Hz).

(*c*) A solution of the β-lactam (14) (100 mg) [obtained by hydrogenation of the non-crystalline isomer of (12)] in methanol (4 ml) and 3N-hydrochloric acid (0.5 ml) was treated with the Hopkins reagent (10% $HgSO_4$ in aqueous 5% H_2SO_4) [15] (1.5 ml). After 3 h the white precipitate was removed by centrifugation, washed with methanol (2 ml), and treated with hydrogen sulphide as described in (*a*) to give a 4-mercapto-β-lactam (15) (47 mg, 60%).

Tritylation of this mercapto-β-lactam (15 mg) under the conditions described in (*a*) afforded a tritylthio-β-lactam (16) (15 mg, 63%), m.p. 174—175° (from methanol). The m.p. was not depressed by mixing with the less polar isomer of the β-lactam (16) described in (*b*).

(*d*) The isomeric β-lactam (14) [obtained from the hydrogenation of the crystalline isomer of (12)] was treated as described in (*c*) to give a tritylthio-β-lactam (16), m.p. 142—143°. The m.p. was not depressed by mixing with the more polar isomer of the β-lactam (16) described in (*a*).

1-(3-*Iodo*-1-*methoxycarbonylpropyl*)-3-*phthalimido*-4-*trityl*-*thioazetidin*-2-*one* (18).—A mixture of the β-lactam (16), m.p. 142—143° (350 mg), sodium iodide (700 mg), and methyl iodide (3 ml) in dimethylformamide (7 ml) was heated under reflux (bath temperature 90°) for 24 h, and then evaporated. The residue was chromatographed (Merck p.l.c. plates) silica gel F_{254}; 2 : 1 v/v hexane–acetone as eluant) to give the β-*lactam* (18) (201 mg, 50%), m.p. 166—167° (from methanol), $\nu_{max.}$ (KBr) 1 789, 1 773, 1 745, and 1 721 cm^{-1}, δ (C_6D_6) 2.45 (2 H, t, *J* 7 H z, CH_2·C*H*$_2$I), 3.1 (2 H, m, CH·C*H*$_2$·CH_2), 3.49 (3 H, s, OMe), 4.26 (1 H, t, *J* 7 Hz, N·C*H*·CO_2Me), 5.19 (1 H, d, *J* 2.5 Hz, ring H), 5.74 (1 H, d, *J* 2.5 Hz, ring H), and 6.7—7.6 (complex, aromatic) (Found: C, 58.4; H, 3.8; N, 3.7; S, 4.6. $C_{35}H_{29}IN_2O_5S$ requires C, 58.7; H, 4.1; N, 3.9; S, 4.5%).

Methyl 7-*Phthalimido*-6,7-trans-DL-*cepham*-4-*carboxylate* (20).—A suspension of the β-lactam (18) (189 mg) in methanol (5 ml) was stirred with mercury(II) chloride (150 mg) for 20 h. The precipitate was filtered off and washed with methanol (2 ml), to give a mercury compound (19) (123 mg), m.p. 158—159° (decomp.). This substance (120 mg) was suspended in dimethylformamide (3 ml); the mixture was stirred at 100—110° for 20 h and then evaporated. Chromatography (Merck p.l.c. plates; silica gel F_{254}; 49 : 1 v/v methylene chloride–acetone as eluant) to give the *bicyclic* β-*lactam* (20) (53 mg, 59%), m.p. 207—208° (from methanol), $\nu_{max.}$ (KBr) 1 785, 1 772, 1 748, and 1 718 cm^{-1}, δ ($CDCl_3$) 2.1 (2 H, m, CH·C*H*$_2$·CH_2), 2.9 (2 H, m, CH_2·C*H*$_2$S), 3.89 (3 H, s, OMe), 4.23 (1 H, t, *J* 7 Hz, N·CH·CO_2Me), 5.15 (1 H, d, *J* 2.5 Hz, ring H), 5.37 (1 H, d, *J* 2.5 Hz, ring H), and 7.85 (4 H, m, aromatic) (Found: C, 55.65; H, 4.1; N, 8.0; S, 9.5. $C_{16}H_{14}N_2O_5S$ requires C, 55.5; H, 4.1; N, 8.1; S, 9.2%), *m/e* 346 (M^+).

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[15] F. G. Hopkins and S. W. Cole, *J. Physiol.*, 1901—1902, **27**, 418.