Studies Related to Penicillins and Cephalosporins. Part III.[1] Oxidative Rearrangement of a 4-Mercaptoazetidin-2-one to a Δ^4-Isothiazolin-3-one†

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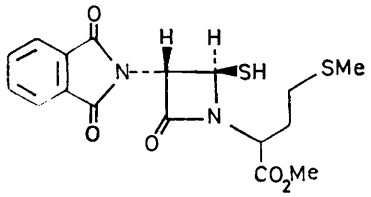
4-(*p*-Methoxybenzylthio)-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-3-phthalimidoazetidin-2-one (16) was obtained in the reaction of *p*-methoxybenzyl *N*-(1-methoxycarbonyl-2-methylprop-1-enyl)thioformimidate (14) with phthaloylglycyl chloride and triethylamine. Removal of the sulphur-protecting group in compound (16) gave the 4-mercapto-β-lactam (17), which underwent oxidative rearrangement to 2-(1-methoxycarbonyl-2-methylprop-1-enyl)-4-phthalimido-Δ^4-isothiazolin-3-one (20) when treated with dimethyl sulphoxide.

ALTHOUGH some mercapto-β-lactams have been suggested as key intermediates in the synthesis of penicillin and cephalosporin analogues,[2] little is known about their chemistry. The 4-mercapto-β-lactam (1), which has a common nitrogen atom with methionine methyl ester was recently synthesized in this laboratory.[3] The 4-mercapto-β-lactams (2) and (3), which have a common nitrogen atom with a didehydrovaline system, have been proposed as intermediates in the biosynthesis of penicillins and cephalosporins.[4] According to this hypothesis the formation of the penicillin nucleus occurs by an intramolecular addition of a thiol grouping to the αβ-unsaturated acid system. The intermediacy of a similar compound [(4) or (5)] has been postulated for the chemical conversion of the anhydropenicillin (7) into the penicillin (8).[5] Mercapto-β-lactams of type (6) might therefore be useful as intermediates in the synthesis of penicillin by a route which mimics in its last step a presumed biogenetic process. We now describe the synthesis and some of the properties of a *trans*-member of this group of compounds, namely the 4-mercapto-β-lactam (17).

Our synthetic approach [1,3] implied the use of the thioformimidate (14) as an intermediate. This compound was prepared from penicillamine by two procedures. In one procedure penicillamine was converted into its S-*p*-methoxybenzyl derivative (78%) by aralkylation in liquid ammonia,[6] and then condensed with *O*-ethyl thioformate. The thioformamide (11) so formed was isolated as its dicyclohexylammonium salt (84%) and then treated with methyl toluene-*p*-sulphonate to give the methyl ester (12) (69%). Treatment of this



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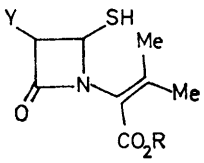
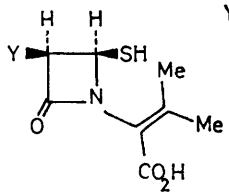
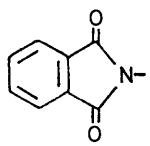
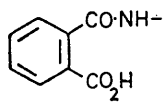


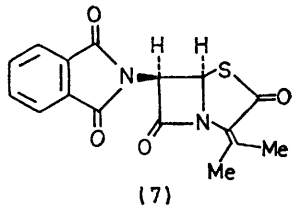
(6) R=H or protecting group
Y= potential amino-group*



(2) Y=δ-(L-α-aminoadipoylamino)
(3) Y=δ-(D-α-aminoadipoylamino)

(4) Y = 

(5) Y = 



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† A summary of this work was presented at the Third International Symposium on Synthesis in Organic Chemistry, Oxford, 1973.

[1] Part II, M. D. Bachi and O. Goldberg, *J.C.S. Perkin I*, 1972, 2332.

[2] J. C. Sheehan, U.S.P. 3,487,074/1969.

[3] M. D. Bachi and K. J. Ross-Petersen, *J.C.S. Chem. Comm.*, 1974, 12.

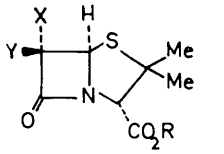
[4] P. A. Lemke and D. R. Brannon in 'Cephalosporins and Penicillins,' ed. E. H. Flynn, Academic Press, New York and London, 1972, p. 370.

[5] S. Wolfe, R. N. Bassett, S. M. Caldwell, and F. I. Wasson, *J. Amer. Chem. Soc.*, 1969, **91**, 7205.

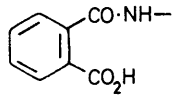
[6] J. E. Wilson and V. Du Vigneaud, *J. Biol. Chem.*, 1950, **184**, 63.

* Protected amino-group(s) which can be converted readily into an amino-group.

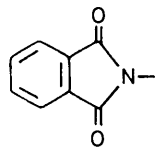
compound with *p*-methoxybenzyl chloride and sodium hydride in benzene gave the thioformimidate (13).



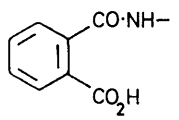
(8) R=X=H, Y=

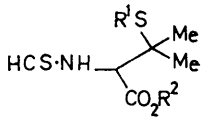


(9) R=Me, Y=H, X=



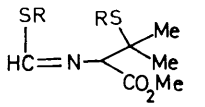
(10) R=Me, Y=H, X=



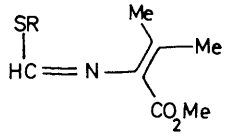


(11) R^1= *p*-MeO·C_6H_4·CH_2, R^2=H

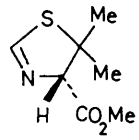
(12) R^1= *p*-MeO·C_6H_4·CH_2, R^2=Me



(13) R=*p*-MeO·C_6H_4·CH_2



(14) R=*p*-MeO·C_6H_4·CH_2



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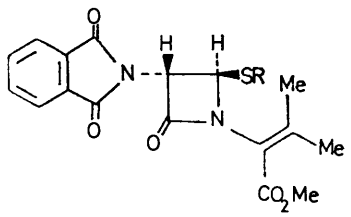
Elimination of 1 molecule of *p*-methoxytoluene-α-thiol to give the thioformimidate of didehydrovaline (14) was effected by sodium hydride in benzene–dimethylformamide. The accompanying sodium *p*-methoxytoluene-α-thiolate was neutralized with an excess of methyl iodide, the inorganic salts and volatile compounds were removed, and the crude thioformimidate (14) was used without further purification. Alternatively, penicillamine methyl ester was condensed with *O*-ethyl thioformate to give the thiazoline (15) [7] in quantitative yield. Treatment of this compound with sodium hydride and *p*-methoxybenzyl chloride resulted in a sort of Michael ring opening and *S*-alkylation to give directly the thioformimidate (14).

The β-lactam (16) was obtained by the interaction of the thioformimidate (14) with phthaloylglycyl chloride and triethylamine, in 30% yield based on the thioformamide (12) by the first described procedure, or in 55% yield based on the thiazoline (15) when the second procedure was used. The sulphur-protecting group was removed by refluxing in trifluoroacetic acid containing silver acetate and anisole. The resulting silver thiolate in chloroform was treated with hydrogen sulphide to give the 4-mercapto-β-lactam (17) (96%). This compound is an amorphous solid, fairly stable under neutral and acidic conditions but highly sensitive to bases both in protic and in aprotic solvents. Tritylation with trityl chloride in chloroform gave the tritylthio-β-lactam (18).

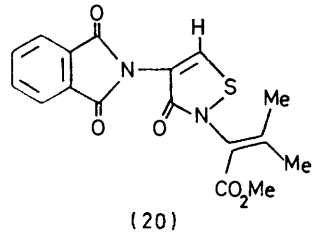
The transformation of the anhydropenicillin (7) into the penicillin (8) has been reported to occur in a mixture of dimethyl sulphoxide and a boric acid–borax buffer (pH 7·4).[5] These reaction conditions were initially considered to be also suitable for the conversion of the 4-mercapto-β-lactam (17) into the *trans*-penicillin (9) or (10). However when the β-lactam (17) was subjected to such a treatment the four-membered ring was cleaved giving a new compound to which structure (20) was assigned (40%). Similar isothiazolinones have been isolated previously from the chlorination of 1,4-thiazepines [8] and from rearrangements of penicillin sulphoxides.[9] The formation of the



(16) R=*p*-MeO·C_6H_4·CH_2

(17) R=H

(18) R=Ph_3C



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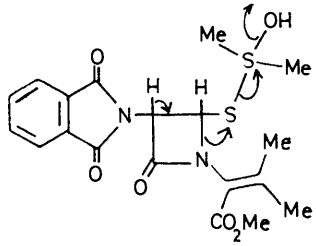

(19)

isothiazoline (20) may be rationalized by a mechanism which involves the participation of dimethyl sulphoxide

[7] M. R. Bell, J. A. Carlson, and R. Oesterlin, *J. Org. Chem.*, 1972, **37**, 2733.

[8] N. J. Leonard and G. E. Wilson, *J. Amer. Chem. Soc.*, 1964, **86**, 5307.

[9] R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, 1969, **91**, 1401; D. H. R. Barton, F. Comer, D. G. T. Greig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc.* (*C*), 1971, 3540.

in an oxidative rearrangement of the 4-mercapto-β-lactam (17), presumably through the intermediate (19). In fact, the isothiazolinone (20) was formed also in pure dimethyl sulphoxide under a nitrogen atmosphere (45% yield) but not in dimethoxyethane, tetrahydrofuran, or dimethylformamide.

Wallace and Mahon [10] suggested on the basis of kinetic studies that a thiol–sulphoxide adduct similar to the proposed intermediate (19) is involved in the oxidation of thiols to disulphides by sulphoxides. Furthermore, they found that the acidity of the thiol greatly affects the ease of oxidation. The failure of the αβ-unsaturated ester (17) to undergo an intramolecular Michael addition is surprising when either of the unsaturated acids (4) and (5), with their less electrophilic double bonds, is considered as an intermediate in the conversion of anhydropenicillin (7) into the penicillin (8).[5] This discrepancy might however be rationalized on the grounds of a decrease in the acidity of the thiol function in the monobasic acid (4) [which would be even greater in the dibasic acid (5)] as compared with the ester (17). Such an effect could inhibit the oxidative rearrangement of the mercapto-β-lactam and thereby enable the competitive intramolecular addition to the double bond. Also the stereochemistry of the β-lactam ring may have some influence on the reaction path. The synthesis of other *trans*- and *cis*-β-lactams of type (6) required for the elucidation of these problems is now being studied.

EXPERIMENTAL

For general experimental details see Part II.[1]

3-(*p-Methoxybenzylthio*)*valine*.—This compound was prepared in a manner similar to that described previously for 3-(methylthio)valine.[6] To a stirred suspension of D-3-mercaptovaline (2·98 g) in liquid ammonia (100 ml), small chips of sodium were added until the blue colour persisted (*ca.* 1 g). This was followed by the dropwise addition of *p*-methoxybenzyl chloride (3·5 g) in benzene (20 ml) and the slow (overnight) evaporation of the ammonia. The residue was treated with water (60 ml) and the resulting turbid solution was filtered, washed with ether (×2), and then brought to pH 6 with concentrated hydrochloric acid. The precipitate (5·4 g) crystallised from water–ethanol to give 3-(p-*methoxybenzylthio*)*valine* (4·2 g, 78%), m.p. 192—195°, δ (D_2O–NaOD) 1·21 (3H, s, CMe), 1·47 (3H, s, CMe), 3·25 (1H, s, N·*CH*·CO_2H), 3·67 and 3·68 (inner lines of ABq, SCH_2) and 3·71 (s, OMe) (5H), 6·83 (2H, d, *J* 9 Hz, ArH), and 7·23 (2H, d, *J* 9 Hz, ArH) (Found: C, 58·2; H, 7·0; N, 5·4; S, 11·75. $C_{13}H_{19}NO_3S$ requires C, 58·0; H, 7·1; N, 5·2; S, 11·9%).

N-*Thioformyl*-3-(p-*methoxybenzylthio*)*valine* (11).—To a stirred suspension of 3-(*p*-methoxybenzylthio)valine (1·08 g) in methanol (40 ml), triethylamine (1·17 g) and *O*-ethyl thioformate (1·93 g) were added. The mixture, which became clear after *ca.* 30 min, was kept for an additional 48 h, then evaporated, and the residue was treated with methanol. The insoluble material was filtered off, the filtrate was evaporated, and the residue was stirred with ice-cold water–ethyl acetate and then acidified (pH 2) with N-hydrochloric acid. The aqueous layer was extracted with more ethyl acetate (×3) and the combined organic fractions were washed with 0·1N-hydrochloric acid followed by water, dried, and evaporated to give the thioformamide (11) (1·42 g), $\nu_{max.}$ ($CHCl_3$) 3340br, 1722, and 1613 cm^{-1}, δ ($CDCl_3$) 1·50 (6H, s, 2CMe), 3·75 (s, SCH_2) and 3·77 (s, OMe) (5H), 5·25 (1H, d, *J* 8·5 Hz, NH·*CH*·CO_2H), 6·78 (2H, d, *J* 9 Hz, ArH), 7·22 (d, *J* 9 Hz, ArH), 7·40br (CO_2H), 8·32br (1H, NH), and 9·55 (1H, d, *J* 6 Hz, HCS). To a stirred solution of the acid (11) in ether (100 ml), dicyclohexylamine (728 mg) in ether (10 ml) was added. The precipitate was filtered off and recrystallized from ethanol to give the *dicyclohexylammonium salt* of the *acid* (11) (1·67 g, 84%), m.p. 191—192° (Found: C, 63·3; H, 8·6; N, 5·4; S, 12·85. $C_{26}H_{42}N_2O_3S_2$ requires C, 63·1; H, 8·6; N, 5·7; S, 12·9%).

N-*Thioformyl*-3-(p-*methoxybenzylthio*)*valine Methyl Ester* (12).—The dicyclohexylammonium salt of the acid (11) (9·88 g) was added to methyl toluene-*p*-sulphonate (3·81 g) in dimethylformamide (200 ml). The mixture was stirred for 20 h, during which the solid went into solution, and then evaporated; the residue was treated with ether and the mixture filtered. The filtrate was washed with water and dried to give, after column chromatography over silica gel, the *ester* (12) (4·51 g, 69%), m.p. 70—71° (from hexane–ethyl acetate), $\nu_{max.}$ ($CHCl_3$) 1745, 1610, and 1510 cm^{-1}, δ ($CDCl_3$) 1·47 (6H, s, 2CMe), 3·77 (s, SCH_2), and 3·80 (s, CO_2Me and OMe) (8H), 5·25 (1H, dd, *J* 0·8 and 8·5 Hz, HCS·NH·*CH*·CO_2Me), 6·87 (2H, d, *J* 9 Hz, ArH), 7·27 (d, *J* 9 Hz, ArH), 8·18br (1H, NH), and 9·50 (1H, dd, *J* 0·8 and 6·0 Hz, HCS) (Found: C, 55·3; H, 6·2; N, 4·0; S, 19·3. $C_{15}H_{21}NO_3S_2$ requires C, 55·0; H, 6·5; N, 4·3; S, 19·55%).

Methyl D-5,5-*Dimethyl*-Δ²-*thiazoline*-4-*carboxylate* (15).—A suspension of D-3-mercaptovaline methyl ester hydrochloride (2·0 g) in ether (50 ml) was treated at 0 °C with triethylamine (1·09 g) and the precipitated triethylammonium chloride was filtered off. The residue obtained after evaporation was dissolved in chloroform (50 ml) and *O*-ethyl thioformate (2 ml) was added at 0 °C. The solution was kept for 6 h at room temperature and then evaporated under reduced pressure to give the thiazoline (15) (1·68 g, 97%) (pure by n.m.r. and t.l.c.). Distillation (55—60° at 0·05 mmHg) afforded a sample of m.p. 46·5—47·5° (lit.,[7] 50·5—51·5°), $[\alpha]_D^{20}$ +56·1° (*c* 1 in $CHCl_3$) (lit.,[7] +51·9°), $\nu_{max.}$ ($CHCl_3$) 1730 and 1570 cm^{-1}, δ ($CDCl_3$) 1·38 (3H, s, CMe), 1·75 (3H, s, CMe), 3·85 (3H, s, CO_2Me), 4·67 (1H, d, *J* 2·75 Hz, N·*CH*·CO_2Me), and 8·19 (1H, d, *J* 2·75 Hz, N:CH·S).

4-(p-*Methoxybenzylthio*)-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-3-*phthalimidoazetidin*-2-*one* (16).—(*a*) The thioformamide (12) (818 mg) in benzene (25 ml) was added in one portion to a stirred suspension of sodium hydride (150 mg; 50% in paraffin). After 15 min *p*-methoxybenzyl chloride (0·5 ml) was added. The mixture was stirred for an additional 45 min and then filtered through Celite. Removal of the solvent and the excess of *p*-methoxybenzyl chloride afforded an oil (1·1 g) which contained *ca.* 65% of the thioformimidate (13), $\nu_{max.}$ ($CHCl_3$), 1740, 1613, 1595, and 1510 cm^{-1}, δ ($CDCl_3$) 8·23 (s, HCS). The crude product and sodium hydride (obtained by washing 1 g of a 50% suspension in paraffin with benzene) in benzene–dimethylformamide (5 : 2 v/v; 28 ml) were stirred for 75 min, during which hydrogen was evolved. Methyl iodide (1·14 g) was added and the mixture was

[10] T. J. Wallace and J. H. Mahon, *J. Amer. Chem. Soc.*, 1964, **86**, 4099.

diluted with benzene, filtered through Celite, and evaporated. Distillation of the residue afforded *p*-methoxybenzylmethyl sulphide (350 mg; 60—75° at 0·015 mmHg) and a second fraction (660 mg; 120—130° at 0·005 mmHg) which was shown by its n.m.r. spectrum [see section (*b*)] to contain 65—70% of the thioformimidate (14). To a stirred solution of this crude thioformimidate and triethylamine (510 mg) in toluene (45 ml), phthaloylglycyl chloride (990 mg) in toluene (45 ml) was added during 2·5 h. The mixture was then filtered and evaporated. Chromatography on a silica gel column (hexane–methylene chloride as eluant) afforded the β-*lactam* (16) (360 mg, 30%), m.p. 132—133° (from hexane–ethyl acetate), $\nu_{max.}$ ($CHCl_3$) 1788sh, 1770, and 1728 cm^{-1}, δ ($CDCl_3$) 2·05 (3H, s, CMe), 2·28 (3H, s, CMe), 3·60 (3H, s, OMe), 3·77 (2H, s, SCH_2Ar), 3·82 (3H, s, CO_2Me), 5·27 (1H, d, *J* 3 Hz, ring H), 5·44 (1H, d, *J* 3 Hz, ring H), 6·66 (2H, d, *J* 9 Hz, ArH), 7·16 (2H, d, *J* 9 Hz, ArH), and 7·82 (4H, m, ArH) (Found: C, 62·4; H, 4·9; N, 5·9; S, 6·55. $C_{25}H_{24}N_2O_6S$ requires C, 62·5; H, 5·0; N, 5·8; S, 6·7%), *m/e* 480 (M^+).

(*b*) The thiazoline (15) (1·73 g) in dimethoxyethane (10 ml) was added at 0° during 45 min to a stirred mixture of *p*-methoxybenzyl chloride (1·57 g) and sodium hydride (0·5 g; 50% in paraffin) in dimethoxyethane (20 ml). The cooling bath was removed and after 35 min the mixture was filtered through Celite and evaporated. The residue was treated with ether, insoluble material was filtered off, and the solution was evaporated to give an oil (2·8 g) which contained *ca.* 70—75% of the thioformimidate (14), $\nu_{max.}$ ($CHCl_3$) 1713, 1613, 1585, 1570, and 1510 cm^{-1}, δ ($CDCl_3$) 1·95 (s, CMe_2), 3·80 (s, CO_2Me and OMe), 4·28 (s, SCH_2), 6·86 (d, *J* 9 Hz, ArH), 7·34 (d, *J* 9 Hz, ArH), and 8·28 (s, HCS). The crude thioformimidate (14) was treated with triethylamine (1·46 g) and phthaloylglycyl chloride (3·0 g) in toluene as described in (*a*). Trituration of the crude product with methyl alcohol gave the β-*lactam* (16) [2·64 g, 55% based on the thiazoline (15)], m.p. 132—133° (from methyl alcohol); spectral data as in (*a*).

4-Mercapto-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-3-phthalimidoazetidin-2-one (17).—A solution of the β-lactam (16) (240 mg), silver acetate (167 mg), and anisole (300 mg) in trifluoroacetic acid (7 ml) was heated to 115° (bath temperature) for 2 min and immediately cooled to 0°. The trifluoroacetic acid was removed under reduced pressure at room temperature and the residue was washed with ether and then dissolved in chloroform. The solution was washed with water until free of silver ions, dried, and evaporated to give the silver salt of the thiol (17) (230 mg), $\nu_{max.}$ ($CHCl_3$) 1782sh, 1766, and 1718 cm^{-1}, δ ($CDCl_3$) 2·15 (s, CMe) and 2·27 (s, CMe) (6H), 3·80 (3H, s, CO_2Me), 5·37 (1H, d, *J* 2 Hz, ring H), 5·67 (1H, d, *J* 2 Hz, ring H), and 7·78 (4H, m, ArH). This was dissolved in chloroform and hydrogen sulphide was passed through the solution. The precipitated silver sulphide was filtered off and the filtrate was evaporated to give the *4-mercapto-β-lactam* (17) (173 mg, 96%), m.p. 155—158°, $\nu_{max.}$ ($CHCl_3$) 1784, 1770, and 1723 cm^{-1}, δ ($CDCl_3$) 2·12 (3H, s, CMe), 2·31 (d, *J* 9·5 Hz, SH), 2·33 (s, CMe) (4H), 3·85 (3H, s, CO_2Me), 5·35 (1H, d, *J* 2·5 Hz, ring 3-H), 5·55 (1H, dd, *J* 2·5 and 9·5 Hz, ring 4-H), and 7·87 (4H, m, ArH) [after addition of D_2O, peak at 2·31 absent and 5·55 peak changed to d (*J* 2·5 Hz)], *m/e* 360 (M^+).

1-(1-Methoxycarbonyl-2-methylprop-1-enyl)-3-phthalimido-4-triphenylmethylthioazetidin-2-one (18).—A solution of the mercapto-β-lactam (17) (514 mg) and trityl chloride (700 mg) in dry chloroform (25 ml) was kept at room temperature during 24 h and then evaporated. The residue was chromatographed on silica gel (preparative thick plates; 3 : 2 v/v benzene–ether) to give the *tritylthio-β-lactam* (18) (430 mg, 50%), m.p. 235—238° (from methyl alcohol), $\nu_{max.}$ ($CHCl_3$) 1783sh, 1768, and 1722 cm^{-1}, δ ($CDCl_3$) 2·08 (3H, s, CMe), 2·45 (3H, s, CMe), 3·78 (3H, s, CO_2Me), 5·18 (1H, d, *J* 2·6 Hz, ring H), 5·37 (1H, d, *J* 2·6 Hz, ring H), 6·83—7·53 (15H, m, Ph_3C), and 7·87 (4H, m, ArH) (Found: C, 71·5; H, 4·8; N, 4·8; S, 5·4. $C_{36}H_{30}N_2O_5S$ requires C, 71·75; H, 5·0; N, 4·65; S, 5·3%), *m/e* 602vw (M^+) and 359 ($M - Ph_3C$).

2-(1-Methoxycarbonyl-2-methylprop-1-enyl)-4-phthalimido-Δ⁴-isothiazolin-3-one (20).—(*a*) The 4-mercapto-β-lactam (17) (738 mg) was added under nitrogen to a stirred mixture [5] of dimethyl sulphoxide (600 ml), water (150 ml), and a boric acid–borax buffer solution (pH 7·4; 150 ml). Complete dissolution of the starting material occurred within 3 h and stirring was continued for an additional 20 h. The solution was then cooled to 0° and shaken with a cold mixture of chloroform (2 l) and water (400 ml). The layers were separated and the aqueous layer was extracted with chloroform (200 ml × 6). The combined organic fractions were washed with water (200 ml × 3), dried, and evaporated. Chromatography (×2) on silica gel thick plates [first ether and then benzene–ethyl acetate–acetone (3 : 2 : 1 v/v/v) as eluant] gave the *isothiazolinone* (20) (295 mg, 40%), m.p. 255—260° (from methanol), $\nu_{max.}$ ($CHCl_3$) 1781, 1730, 1715sh, and 1675 cm^{-1}, $\lambda_{max.}$ (EtOH) 292 nm (ε 13,000), δ ($CDCl_3$) 1·97 (3H, s, CMe), 2·41 (3H, s, CMe), 3·80 (3H, s, CO_2Me), 7·94 (4H, m, ArH), and 8·48 (1H, s, CH) (Found: C, 56·75; H, 4·0; N, 7·7; S, 8·9. $C_{17}H_{14}N_2O_5S$ requires C, 57·0; H, 3·9; N, 7·8; S, 8·9%), *m/e* 358 (M^+).

(*b*) A solution of the 4-mercapto-β-lactam (17) (80 mg) in dimethyl sulphoxide (20 ml) was kept under nitrogen for 20 h. The residue obtained after removal of the solvent under reduced pressure was treated with a mixture of water and ether. The layers were separated and the aqueous fraction extracted with ether (×2). The combined ethereal extracts were washed with water (×5), dried, and evaporated. Purification of the residue as described in (*a*) afforded the isothiazolinone (20) (36 mg, 45%); spectral data as in (*a*).

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