Studies Related to Penicillins and Cephalosporins. Part I. The Preparation of 4-Alkylthio-β-lactams in which the Ring Nitrogen Atom is Part of an α-Amino-acid Ester System

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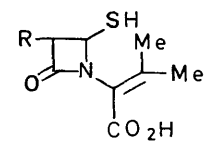
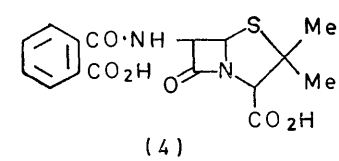
Alkyl thiobenzimidates in which the nitrogen atom is derived from the methyl ester of glycine (7), DL-valine (8), or didehydrovaline [(14) and (19)] undergo cycloaddition with diphenylketen to give the respective *N*-substituted 4-alkylthio-3,3,4-triphenylazetidin-2-ones (20)—(23). The methyl thiobenzimidate derivative (14) of didehydrovaline was conveniently prepared by ring cleavage of methyl 5,5-dimethyl-2-phenyl-Δ^2-thiazoline-4-carboxylate (16) followed by *S*-alkylation of the intermediate thioenolate ion (13). The 2-methoxycarbonylethyl thiobenzimidate (19) was obtained in an exchange reaction with (14). The interconversion of the thiazoline ester (16) and 4-isopropylidene-2-phenyl-Δ^2-thiazolin-5-one (12) and the base-induced degradation of 4-(2-methoxycarbonylethylthio)-1-(1-methoxycarbonyl-2-methylprop-1-enyl)-3,3,4-triphenylazetidin-2-one (23) are described.

THE 4-mercapto-β-lactams (1) and (2) have been proposed as intermediates in the biosynthesis of penicillins and cephalosporins.[1] Derivatives of the lactam (1) have been formed in a reverse Michael opening of the penicillin thiazolidine ring,[2] and in Pummerer-type rearrangements of penicillin sulphoxides.[3] The penicillin (4) has been recently obtained in a non-enzymic reaction which involves the 4-mercapto-β-lactam (3) as an intermediate.[4] The synthesis of β-lactams structurally related to (1) would therefore be expected to provide substrates for a biogenetic-type synthesis [5] of penicillin and similar compounds.





(4)

(1) R = NH_2

(2) R = D-α-aminoadipoyl

(3) R = $C_6H_4(CO)_2N$

Compounds (1)—(3) are formally β-lactams built on the nitrogen atom of didehydrovaline. As a preparatory

[1] E. P. Abraham and G. G. F. Newton, in 'Antibiotics,' eds. D. Gottlieb and P. D. Shaw, Springer-Verlag, New York, 1967, vol. 2, p. 1.

[2] J. P. Clayton, J. H. C. Nayler, R. Southgate, and P. Toliday, *Chem. Comm.*, 1971, 590.

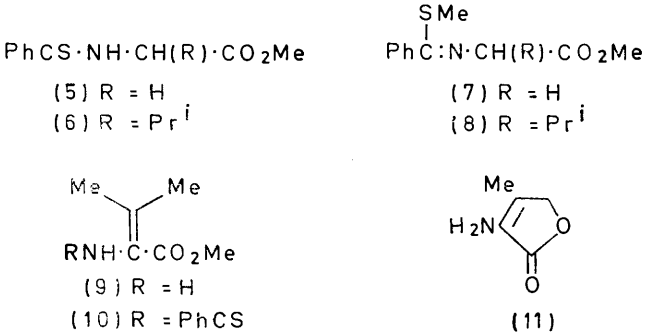
[3] D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *Chem. Comm.*, 1970, 1683; L. D. Hatfield, J. Fischer, F. L. Jose, and R. D. G. Cooper, *Tetrahedron Letters*, 1970, 4897; D. H. R. Barton, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, B. E. Looker, and W. G. E. Underwood, *Chem. Comm.*, 1971, 1137.

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

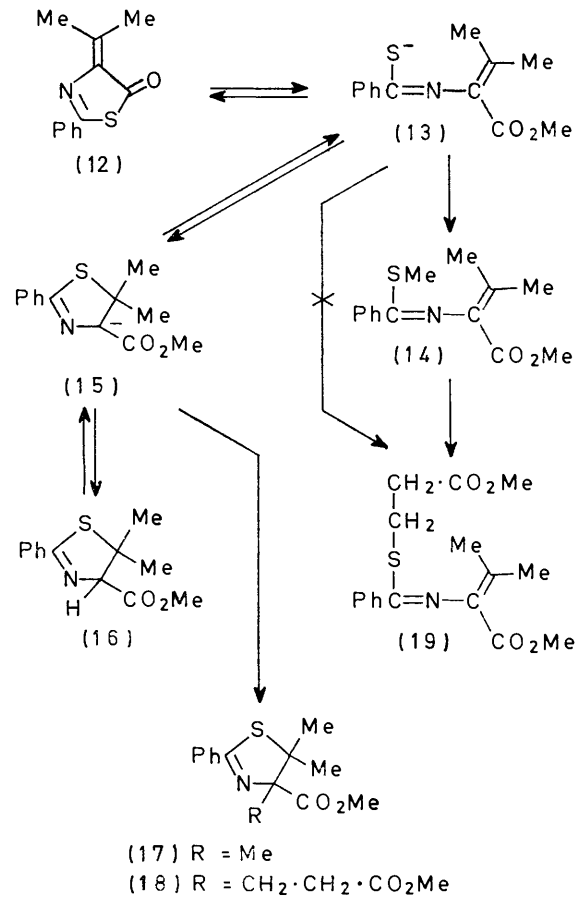
[5] E. E. van Tamelen, *Progr. Chem. Org. Natural Products*, 1961, **19**, 242.

study for the synthesis of these and other β-lactams related to penicillin,[6] we have investigated the applicability of Staudinger's [7] method (for the preparation of β-lactams from ketens and imines) to the preparation of 4-thio-substituted β-lactams wherein the ring nitrogen atom is part of an α-amino-acid system. It has already been shown that ketens undergo cycloaddition not only with *N*-arylidenearylamines as was originally assumed, but also with other compounds bearing a carbon–nitrogen double bond.[8-11] For example, 3,3-dimethyl-1,4-diphenyl-4-methylthioazetidin-2-one was obtained from dimethylketen and methyl (*N*-phenyl)thiobenzimidate,[9] and several bicyclic β-lactams were obtained from diphenylketen and 2-substituted Δ^2-thiazolines.[10,11] However, these reactions, which are strongly influenced by the nature of the substituents next to the carbon–nitrogen double bond and by the reaction conditions, sometimes take alternative courses which do not lead to β-lactams.[8,11-13] We now show that thiobenzimidate derivatives of some α-amino-acids are useful intermediates in the synthesis of β-lactams.

The methyl esters of *N*-thiobenzoylglycine (5) and *N*-thiobenzoyl-DL-valine (6) were prepared by thiobenzoylation [14] of the corresponding α-amino-acid esters with sodium (thiobenzoylthio)acetate.[15] Treatment of these thiobenzamides with sodium hydride in tetrahydrofuran followed by alkylation with methyl iodide afforded the methyl thiobenzimidates (7) and (8). Didehydrovaline methyl ester (9) which was considered as a possible starting material for the preparation of the thiobenzamide (10) was not suitable, owing to the poor nucleophilic character of its amino-group. It has been previously reported [16] that the similar enamine (11) undergoes thiobenzoylation at a very low rate. Attempts to prepare thiobenzoyldidehydrovaline methyl



ester (10) by methanolysis of the isopropylidene-thiazolinone (12) under various neutral, acidic, or basic conditions gave methyl 5,5-dimethyl-2-phenyl-Δ^2-thiazoline-4-carboxylate (16). For example this thiazoline was formed in high yield upon heating (12) under reflux in methanol containing 1 equiv. of sodium methoxide. The thioenolate ion (13) must be an intermediate in this reaction. Thus, when the reaction was repeated in the presence of an excess of methyl iodide the desired thioimidate (14) was obtained directly (26%). Attempts to increase the yield in the *S*-alkylation of (13) at the expense of the competing conjugated intramolecular thiolate addition [formation of (16)] were limited by the conditions required for the methanolysis of (12). We therefore planned to generate the thioenolate ion



(13) by ring cleavage of the thiazoline (16), which already contains the methoxycarbonyl grouping. On addition of compound (16) at −10° to a suspension of an excess of sodium hydride in tetrahydrofuran containing an excess of methyl iodide, hydrogen was evolved, and the

[6] M. D. Bachi and O. Goldberg, *J.C.S. Chem. Comm.*, 1972, 319; following paper.
[7] H. Staudinger, *Annalen*, 1907, **356**, 51.
[8] J. C. Sheehan and E. J. Corey, *Org. Reactions*, 1957, **9**, 388.
[9] A. D. Holley and R. W. Holley, *J. Amer. Chem. Soc.*, 1951, **73**, 3172.
[10] 'The Chemistry of Penicillin,' eds. H. T. Clarke, J. R. Johnson, and R. Robinson, Princeton Univ. Press, Princeton, 1949, p. 973.
[11] R. Pfleger and A. Jäeger, *Chem. Ber.*, 1957, **90**, 2460.
[12] H. Staudinger, H. W. Klever, and P. Kober, *Annalen*, 1910, **374**, 1; J. C. Martin, A. V. Hoyle, and K. C. Brannock, *Tetrahedron Letters*, 1965, 3589; R. N. Pratt, G. A. Taylor, and S. A. Proctot, *J. Chem. Soc.* (*C*), 1967, 1569; R. Huisgen, B. A. Davis, and M. Morikawa, *Angew. Chem. Internat. Edn.*, 1968, **7**, 826; J. C. Martin, K. C. Brannock, R. D. Burpitt, P. G. Gott, and V. A. Hoyle, *J. Org. Chem.*, 1971, **36**, 2211.
[13] M. D. Bachi, *J.C.S. Perkin I*, 1972, 310.
[14] (*a*) A. Kjaer, *Acta Chem. Scand.*, 1950, **4**, 1347; (*b*) E. Bach and A. Kjaer, *ibid.*, 1966, **20**, 2781.
[15] F. Kurzer and A. Lawson, *Org. Synth.*, 1962, **42**, 100.
[16] G. C. Barrett, V. V. Kane, and G. Lowe, *J. Chem. Soc.*, 1964, 783.

resulting carbanion (15) was trapped by the methyl iodide, giving the trimethylthiazoline (17) (67%). At room temperature and in the absence of an alkylating agent, the initially formed carbanion (15) rearranged to the thioenolate ion (13), which on ring closure with concomitant displacement of methoxide ion gave the thiazolinone (12) (68%); thus the reaction by which (12) was originally converted into (16) was reversed. When the thiazoline (16) was added to a suspension of 1 equiv. of sodium hydride in dimethoxyethane at 0°, followed by 1·1 equiv. of methyl iodide the methyl thioimidate (14) was obtained (70%). The same thioimidate was formed (75%) when potassium t-butoxide was employed in the same solvent at −15°. Attempts to convert the thiazoline (16) into the 2-methoxycarbonylethyl thiobenzimidate (19) by use of methyl 3-bromopropionate instead of methyl iodide as the alkylating agent afforded the *C*-alkylated product (18) (35%); no *S*-alkylated product was isolated. The thioimidate (19) was eventually obtained in an exchange reaction by warming the thioimidate (14) with methyl 3-mercaptopropionate (78%).

The n.m.r. spectrum of the thioimidate (7) in deuteriochloroform shows two sharp singlets for each methyl group and two distinct doublets for the α-protons (see Table). An analogous pattern is observed for the thioimidate (8). The appearance of two sets of signals in the spectra of these thioimidates indicates the presence of *syn*- and *anti*-isomers, (A) and (B).[17] In the n.m.r. spectrum of compound (14) one of the vinylic methyl groups appears as a sharp singlet while the other groups give very broad signals, indicating that the coalescence temperature coincides in this case with room temperature.* The decrease in the energy barrier for *syn–anti* isomerization of (14) as compared to (8) is attributed to the presence of the conjugated double bond. This is in accord with the previously reported greater isomerization rate of some *N*-phenyl imines [17a,b] and *N*-cyano-imines [17c] as compared to *N*-alkyl imines having the same *C*-substituents. The n.m.r. spectra of protonated (14) exhibits two sets of signals derived from the *syn*- and *anti*-isomers.[17d] As shown in the Table, the thioimidate (19) gives rise to similar n.m.r. patterns.

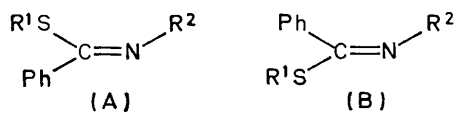
When treated with diphenylketen the thioimidate (7) was converted into the β-lactam (20) (69%), and the thioimidate (8) gave two diastereoisomers of the β-lactam (21) (72%). Similarly, addition of diphenylketen to the thioimidates (14) and (19) under high dilution conditions [18] afforded the β-lactams (22) (61%) and (23) (53%). The mass spectra of the β-lactams (20)—(23) exhibit molecular ion peaks, but, except for (20), these peaks are of very low relative intensity. The characteristic [19] fissions a and b [see formula (C)] give rise to the fragments (D) and (F) in all the spectra. Fragment (E) is present only in the spectra of (22) and (23), peaks corresponding to the ion (G) are a common feature of all four β-lactams.

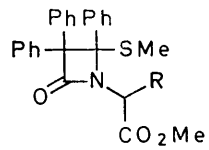
Since it is known that methyl 6-phthalimidopenicil-

^{1}H N.m.r. data [a] for the thiobenzimidates (7), (8), (14), and (19) (δ values in p.p.m.)

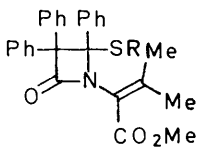
	CαH		OMe		OMe [b]		SMe		C:CMe		C:CMe		(a) : (b) [c]
Compound	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	
(7)	4·17(s)	4·48(s)	3·72(s)	3·80(s)			2·47(s)	2·12(s)					1·3 : 1
(8)	3·87 (d, *J* 6·0 Hz)	4·50 (d, *J* 6·5 Hz)	3·68(s)	3·75(s)			2·45(s)	2·10(s)					1·8 : 1
(14)			3·5br				2·4br		2·1br		1·78(s)		
(14)H$^+$ [d]			3·87(s)	3·67(s)			2·48(s) or 2·42(s)	2·97(s)	2·42(s) or 2·48(s)	2·15(s)	2·03(s)	1·97(s)	2·2 : 1
(19)			3·5br		3·68(s)				2·0br		1·73(s)		
(19)H$^+$ [d]			3·75(s)	3·65(s)	3·92(s)	3·87(s)			2·43(s)	2·22(s) or 2·13(s)	2·03(s)	2·13(s) or 2·22(s)	1·3 : 1

[a] Recorded with a Varian A60 spectrometer for solutions in deuteriochloroform. [b] Attributed to $CH_2{\cdot}CH_2{\cdot}CO_2Me$. [c] Represents the relative hydrogen content of the signals (a) of one isomer to the signals (b) of the other isomer; [d] Protonation by addition of a few drops of trifluoroacetic acid.





(20) R = H
(21) R = Pr^i



(22) R = Me
(23) R = $CH_2{\cdot}CH_2{\cdot}CO_2Me$

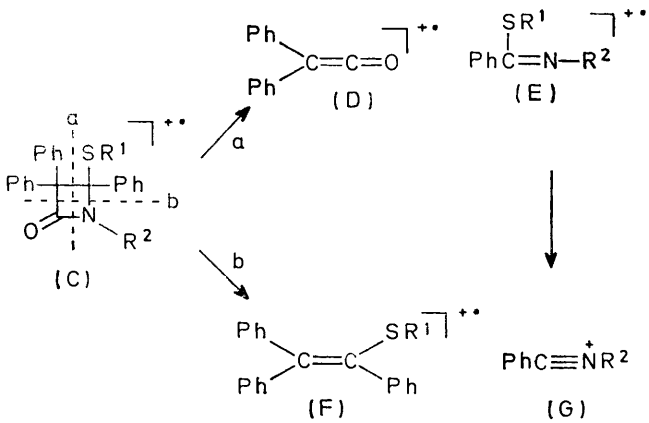
* This postulate has been confirmed by a variable temperature ^{1}H n.m.r. study.

[17] For illustrative studies about the correlation between the *syn–anti* isomerisation and the n.m.r. spectra of imino-compounds see: (*a*) D. Y. Curtin and C. G. McCarty, *Tetrahedron Letters*, 1962, 1269; D. Y. Curtin, E. J. Grubbs, and C. G. McCarty, *J. Amer. Chem. Soc.*, 1966, **88**, 2775; (*b*) D. Wurmb-Gerlich, F. Vögtle, A. Mannschreck, and H. A. Staab, *Annalen*, 1967, **708**, 36; (*c*) C. G. McCarty and D. M. Wieland, *Tetrahedron Letters*, 1967, 1787; (*d*) F. Vogtle, A. Mannschreck, and H. A. Staab, *Annalen*, 1967, **708**, 51.

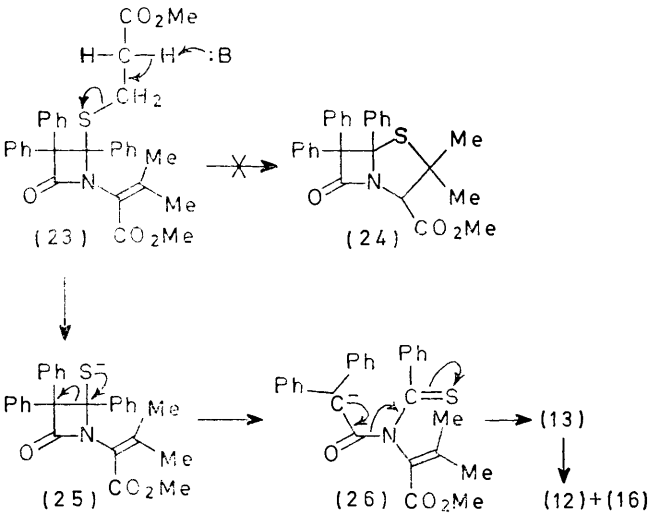
[18] A. C. Cope and E. C. Herrick, *J. Amer. Chem. Soc.*, 1950, **72**, 983.

[19] H. E. Audier, M. Fétizon, H. B. Kagan, and J. L. Luche, *Bull. Soc., chim. France*, 1967, 2297; A. K. Bose and I. Kugajevsky, *Tetrahedron*, 1967, **23**, 957; M. B. Jackson, T. M. Spotswood, and J. H. Bowie, *Org. Mass Spectrometry*, 1968, **1**, 857.

lanate preserves its bicyclic β-lactam structure on treatment with sodium hydride in tetrahydrofuran or with potassium t-butoxide in t-butanol,[20] we considered that a base-induced β-elimination of methyl acrylate from structure (23) would lead to the thiolate anion (25),



which might undergo ring closure to the penam (24). However, when compound (23) was treated with potassium t-butoxide in dimethoxyethane, degradation took place and none of the products contained a β-lactam structure. In addition to unidentified substances having a high phenyl content, the thiazolinone (12), the thiazoline (16), and methyl diphenylacetate were isolated. The yields were strongly influenced by the reaction conditions, probably owing to secondary processes which occurred on prolonged exposure to the basic reagent. It is suggested that the base-induced degradation of (23) takes place as shown in the Scheme.



SCHEME

The fate of the major part of the diphenylketen system was not elucidated; a minor part reacted with methoxide ion [formed during the cyclization of (13) to (12)] to give methyl diphenylacetate. The conversions of the intermediate (13) into compounds (12) and (16) have already been discussed.

The preponderance of this degradation process over the conjugated thiolate addition which would give the penan (24) in the same manner as in the cyclization (3) ⟶ (4) [4] seems to be a consequence of the driving force exerted by the stabilization of the intermediate carbanion (26) by the delocalization of the negative charge over a carbonyl and two phenyl groups.

EXPERIMENTAL

M.p.s were determined with a Büchi apparatus. I.r. spectra were obtained with a Perkin-Elmer Infracord spectrometer. N.m.r. data were obtained with a Varian A60 spectrometer, tetramethylsilane being used as internal standard. Mass spectra were recorded on an Atlas MAT CH4 spectrometer. The reactions were performed under nitrogen in dry solvents. Evaporations were carried out with a rotary evaporator under reduced pressure.

N-Thiobenzoylglycine Methyl Ester (5).—Glycine methyl ester was treated with (thiobenzoylthio)acetate [15] as previously [14a] described to give the thiobenzamide (5), m.p. 70—71° (lit.,[14a] 73—74°), $\nu_{max.}$ ($CHCl_3$) 2·91 and 5·72 μm, δ ($CDCl_3$), 3·80 (3H, s, OMe), 4·56 (2H, d, *J* 5 Hz, N·C*H*$_2$·CO_2Me), 7·3—7·5 (3H, m, Ph), 7·7—7·9 (2H, m, Ph), and 8·25br (1H, NH).

*N-Thiobenzoyl-*DL*-valine Methyl Ester* (6).—DL-Valine methyl ester was treated with (thiobenzoylthio)acetate,[15] as previously [14a] described for the preparation of (5), to give the thioamide (6) (51%), m.p. 112—113° [lit.,[14b] for L-(6), oil], $\nu_{max.}$ (KBr) 3·08 and 5·83 μm, δ ($CDCl_3$) 1·01 (d, *J* 7 Hz, CH*Me*) and 1·09 (d, *J* 7 Hz, CH*Me*) (6H), 2·1—2·7 (1H, m, C*H*Me$_2$), 3·77 (3H, s, OMe), 5·31 (1H, dd, *J* 8·5 and 8 Hz, N·C*H*·CO_2Me), 7·3—7·5 (3H, m, Ph), 7·7—7·9 (2H, m, Ph), and 8·1br (1H, NH) (Found: C, 62·3; H, 6·9; N, 5·45; S, 12·6. Calc. for $C_{13}H_{17}NO_2S$: C, 62·1; H, 6·8; N, 5·6; S, 12·7%).

Methyl N-(*Methoxycarbonylmethyl*)*thiobenzimidate* (7).—*N*-Thiobenzoylglycine methyl ester (5) (9·4 g) in tetrahydrofuran (100 ml) was added during 10 min to a suspension of sodium hydride (1·08 g) in tetrahydrofuran (100 ml). The mixture was stirred for 1 h at room temperature and then methyl iodide (8·0 g) in tetrahydrofuran (50 ml) was added. After being stirred overnight the mixture was filtered through Celite and evaporated; a solution of the residue in ether was washed with water. The residue (8·66 g) obtained after removal of the ether was distilled (115—116° at 0·2 mmHg) to give the *thioimidate* (7) (7·62 g, 76%), $\nu_{max.}$ (CCl_4) 5·70, 6·18, and 6·27 μm, n.m.r. see Table (Found: C, 59·5; H, 6·0; N, 6·1; S, 14·5. $C_{11}H_{13}NO_2S$ requires C, 59·2; H, 5·9; N, 6·3; S, 14·3%, *m/e* 223 (M^+).

Methyl N-(1-*Methoxycarbonyl*-2-*methylpropyl*)*thiobenzimidate* (8).—*N*-Thiobenzoyl-DL-valine methyl ester (7·0 g) was treated with sodium hydride (0·67 g) and methyl iodide (5·0 g) as described for the preparation of (7). The crude product (6·5 g) was distilled (107—108° at 0·2 mmHg) to give the *thioimidate* (8) (5·3 g, 72%), $\nu_{max.}$ (film) 5·75, 6·19, and 6·28 μm, n.m.r. see Table (Found: C, 63·6; H, 7·15; N, 5·4; S, 11·8. $C_{14}H_{19}NO_2S$ requires C, 63·4; H, 7·2; N, 5·3; S, 12·1%).

Methanolysis of 4-*Isopropylidene*-2-*phenyl*-Δ^2-*thiazolin*-5-*one* (12).—A solution of the thiazolinone (12) [13] (5·43 g)

[20] S. Wolfe and W. S. Lee, *Chem. Comm.*, 1968, 242.

and sodium methoxide [from sodium (0·58 g)] in methanol (200 ml) was warmed under reflux during 20 min, then cooled to 0°, and neutralized with glacial acetic acid (1·5 ml). The solvent was evaporated off and a solution of the residue in ether was washed with cold saturated sodium chloride solution, dried, and filtered. Evaporation afforded an oil which was distilled (115—120° at 0·05 mmHg) (lit.,[21a] 150—154° at 0·5 mmHg) to give the thiazoline (16) (5·2 g, 83%). $\nu_{max.}$ (film) 5·70, 5·79, 6·26, and 6·34 μm, δ ($CDCl_3$), 1·46 (3H, s, CMe), 1·78 (3H, s, CMe), 3·82 (3H, s, OMe), 4·87 (1H, s, CH), 7·3—7·5 (3H, m, Ph), and 7·8—8·0 (2H, m, Ph) (Found: C, 62·65; H, 6·0; N, 5·7; S, 12·6. Calc. for $C_{13}H_{15}NO_2S$: C, 62·6; H, 6·1; N, 5·6; S, 12·8%); picrate, m.p. 106° (from ethanol) (lit.,[21a] 109°; lit.,[21b] 106°).

Methyl N-(1-*Methoxycarbonyl*-2-*methylprop*-1-*enyl*)*thiobenzimidate* (14).—(*a*) A solution of the thiazolinone (12) (2·17 g) in tetrahydrofuran (40 ml) was added at −10° to a solution of sodium methoxide [from sodium (0·23 g)] in methanol (20 ml). After 10 min methyl iodide (7·1 g) was added dropwise during 20 min. The mixture was kept for an additional 1 h at −10° and then for 24 h at room temperature. The residue obtained after evaporation of the methanol was treated with hexane (500 ml) and water (10 ml). The organic layer was washed with brine, dried, filtered, and evaporated. Distillation of the residue (115—120° at 0·2 mmHg) afforded the *methyl thiobenzimidate* (14) (0·69 g, 26%), m.p. 76° (from hexane), $\nu_{max.}$ (KBr) 5·79, 6·22, and 6·33 μm, n.m.r. see Table (Found: C, 63·95; H, 6·5; N, 5·3; S, 11·9. $C_{14}H_{17}NO_2S$ requires C, 63·9; H, 6·5; N, 5·3; S, 12·2%), *m/e* 263 (M^+). When only 2 equiv. of methyl iodide were employed, the distillate was contaminated by the thiazoline (16). The product was then purified by preparative t.l.c. on silica gel (Merck GF_{254}) plates [developed with hexane–ethyl acetate (8 : 1 v/v)].

(*b*) A solution of the thiazoline (16) (4·98 g) in dry dimethoxyethane (50 ml) was added at 0° to a stirred suspension of sodium hydride (504 mg) in dimethoxyethane (50 ml). When the hydrogen evolution ceased (*ca.* 90 min) methyl iodide (3·27 g) was added and stirring was continued for an additional 3 h. The mixture was then filtered through Celite and evaporated. A solution of the residue in ether was washed with cold brine, dried, filtered, and evaporated to give the *thiobenzimidate* (14) (3·69 g, 70%), m.p. and spectral data as in (*a*).

(*c*) A solution of the thiazoline (16) (4·98 g) in dimethoxyethane (40 ml) was added at −15° to a stirred solution of potassium t-butoxide (2·46 g) in dimethoxyethane (70 ml). The mixture acquired an orange colour; after 10 min methyl iodide (3·42 g) in dimethoxyethane (10 ml) was added during 15 min., and stirring was continued for an additional 2 h. The residue obtained after the evaporation of the solvent was taken up with benzene; the solution was washed with cold brine, dried, filtered, and evaporated to give the *thiobenzimidate* (14) (3·93 g, 75%), m.p. and spectral data as in (*a*).

Action of Sodium Hydride on Methyl 5,5-*Dimethyl*-2-*phenyl*-Δ²-*thiazoline*-4-*carboxylate* (16).—A solution of the ester (16) (249 mg) in tetrahydrofuran (2 ml) was added at room temperature to a stirred suspension of sodium hydride (84 mg) in tetrahydrofuran (3 ml). After 90 min the mixture was cooled to −10°, neutralized with acetic acid and evaporated. The residue was taken up with ethyl acetate; the solution was washed with brine, dried, filtered, and evaporated. Recrystallization from ethanol gave the thiazolinone (12) (147 mg, 68%), m.p. 99° (lit.,[13] 99°), identical (spectral data and t.l.c.) with an authentic sample.[13]

Methyl 4,5,5-*Trimethyl*-2-*phenyl*-Δ²-*thiazoline*-4-*carboxylate* (17).—A solution of compound (16) (2·49 g) in tetrahydrofuran (30 ml) was added during 15 min at −15° to a stirred mixture of sodium hydride (0·84 g) and methyl iodide (10·3 g) in tetrahydrofuran (20 ml). The mixture was stirred for an additional 30 min at −15° and for 2 h at room temperature, filtered through Celite, and evaporated. The residue was dissolved in ether; the solution was washed with cold brine, dried, filtered, and evaporated. Chromatography on silica gel (150 g) with benzene–chloroform (1 : 1 v/v) as eluant afforded the *thiazoline* (17) (1·77 g, 67%), m.p. 48° (from hexane), $\nu_{max.}$ ($CHCl_3$) 5·80, 5·74sh, 6·27, and 6·35 μm, δ ($CDCl_3$), 1·45 (3H, s, CMe), 1·53 (3H, s, CMe), 1·68 (3H, s, CMe), 3·80 (3H, s, OMe), 7·3—7·5 (3H, m, Ph), and 7·7—7·9 (2H, m, Ph) (Found: C, 63·9; H, 6·3; N, 5·3; S, 12·3. $C_{14}H_{17}NO_2S$ requires C, 63·9; H, 6·5; N, 5·3; S, 12·2%), *m/e* 263 (M^+).

Methyl 4-(2-*Methoxycarbonylethyl*)-5,5-*dimethyl*-2-*phenyl*-Δ²-*thiazoline*-4-*carboxylate* (18).—A solution of the thiazoline (16) (498 mg) in dry dimethoxyethane (5 ml) was added with stirring at 0° to a suspension of sodium hydride (50 mg) in dimethoxyethane (55 ml). The mixture acquired an orange colour; after 90 min methyl 3-bromopropionate (351 mg) was added and the stirring was continued for an additional 3 h. The mixture was filtered through Celite and evaporated; the residue was dissolved in ether, washed with brine, dried, filtered, and evaporated Preparative t.l.c. on silica gel (Merck GF_{254}) with hexane–ethyl acetate (6 : 1 v/v) as eluant afforded two fractions: a less polar fraction consisting of starting material (16) (155 mg, 31% recovery), and the *thiazoline* (18) (230 mg, 34%), m.p. 47° (from hexane–propan-2-ol), $\nu_{max.}$ (CCl_4) 5·72, 5·75sh, 6·22, and 6·31 μm, δ ($CDCl_3$), 1·42 (3H, s, CMe), 1·68 (3H, s, CMe), 2·2—2·8 (4H, m, $CH_2{\cdot}CH_2$), 3·61 (3H, s, OMe), 3·81 (3H, s, OMe), 7·3—7·5 (3H, m, Ph), and 7·75—7·9 (2H, m, Ph) (Found: C, 61·1; H, 6·4; N, 4·0; S, 9·6. $C_{17}H_{21}NO_4S$ requires C, 60·9; H, 6·3; N, 4·2; S, 9·55%), *m/e* 335 (M^+).

2-*Methoxycarbonylethyl* N-(1-*Methoxycarbonyl*-2-*methylprop*-1-*enyl*)*thiobenzimidate* (19).—A mixture of the methyl thioimidate (14) (5·26 g) and methyl 3-mercaptopropionate (7·20 g) was warmed at 120° for 20 h. Methanethiol was evolved and the residue was chromatographed on a silica gel column (300 g), with hexane–ethyl acetate (8 : 1 v/v) as eluant, to give the 2-*methoxycarbonylethyl thioimidate* (19) (5·23 g, 75%). Distillation (155° at 0·05 mmHg) gave a sample with $\nu_{max.}$ (film) 5·73, 5·81, 6·27, and 6·34 μm, n.m.r. see Table (Found: C, 60·65; H, 6·2; S, 9·8. $C_{17}H_{21}NO_4S$ requires C, 60·9; H, 6·3; S, 9·55%).

1-*Methoxycarbonylmethyl*-4-*methylthio*-3,3,4-*triphenylazetidin*-2-*one* (20).—To a solution of the thioimidate (7) (5·75 g) in toluene (100 ml) a solution of diphenylketen (4·85 g) in toluene (100 ml) was added with stirring during 1 h. After 16 h the solvent was evaporated off and the residue was recrystallized from propan-2-ol–hexane to give the β-*lactam* (20) (7·19 g, 67%), m.p. 137—138°, $\nu_{max.}$ (KBr) 5·63 and 5·71 μm, δ ($CDCl_3$) 1·45 (3H, s, SMe), 3·85 (3H, s, OMe), 4·20 (2H, s, $N{\cdot}CH_2{\cdot}CO_2Me$), 6·9—7·6 (13H, complex, Ph), and 8·0—8·2 (2H, m, Ph) (Found: C, 72·0; H, 5·7; N,

[21] (*a*) Ref. 10, p. 471; (*b*) J. C. Sheehan, H. W. Hill, and E. L. Buhle, *J. Amer. Chem. Soc.*, 1951, **73**, 4373.

3·2; S, 7·6. $C_{25}H_{23}NO_3S$ requires C, 71·9; H, 5·55; N, 3·4; S, 7·7%), *m/e* 417 (M^+) (15%), 302 (0·7), 194 (100), and 176 (16).

1-(1-*Methoxycarbonyl*-2-*methylpropyl*)-4-*methylthio*-3,3,4-*triphenylazetidin*-2-*one* (21).—To a boiling solution of the thioimidate (8) (1·06 g) in benzene (100 ml), diphenylketen (0·98 g) in benzene (40 ml) was added during 6 h through a high dilution cycle.[18] The mixture was warmed under reflux for an additional 20 h and then evaporated. Preparative silica gel t.l.c. [elution with hexane–ethyl acetate (8 : 1 v/v)] afforded the β-*lactam* (21) (1·32 g, 72%), m.p. 135—150° (from benzene–hexane), $\nu_{max.}$ (CS_2), 5·69 and 5·77sh μm, δ ($CDCl_3$) 1·07 (d, *J* 6 Hz), 1·14 (d, *J* 6 Hz), 1·27 (d, *J* 6 Hz), and 1·49 (d, *J* 6 Hz) (total 6 H, $CHMe_2$), 1·65 (s) and 1·73 (s) (3H, SMe), 3·67 (s) and 3·75 (s) (3H, OMe), 6·8—7·5 (13H, complex, Ph), and 7·8—8·1 (2H, m, Ph) (Found: C, 73·1; H, 6·5; N, 2·8; S, 7·0. $C_{28}H_{29}NO_3S$ requires C, 73·2; H, 6·4; N, 3·05; S, 7·0%), *m/e* 459 (M^+) (2%), 302 (2), 218 (37), 194 (100), and 165 (25).

1-(1-*Methoxycarbonyl*-2-*methylprop*-1-*enyl*)-4-*methylthio*-3,3,4-*triphenylazetidin*-2-*one* (22).—Treatment of a solution of the thioimidate (14) (526 mg) in benzene (25 ml) with diphenylketen (582 mg) in benzene (25 ml) under the conditions described for the preparation of (21) afforded, after preparative t.l.c., the β-*lactam* (22) (578 mg, 63%), m.p. 118° (from hexane–propan-2-ol), $\nu_{max.}$ (KBr) 5·69 and 5·76 μm, δ ($CDCl_3$) 1·73 (3H, s, SMe), 2·00 (3H, s, C:CMe), 2·18 (3H, s, C:CMe), 3·57 (3H, s, OMe), 6·9—7·5 (13H, complex, Ph), and 7·8—8·0 (2H, m, Ph) (Found: C, 73·6; H, 5·8; N, 3·2; S, 7·2. $C_{28}H_{27}NO_3S$ requires C, 73·5; H, 5·95; N, 3·1; S, 7·0%), *m/e* 457 (M^+) (1%), 302 (5), 263 (51), 216 (100), 194 (16), and 165 (43).

4-(2-*Methoxycarbonylethylthio*)-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-3,3,4-*triphenylazetidin*-2-*one* (23).—To a boiling solution of the thioimidate (19) (3·35 g) in benzene (150 ml), diphenylketen (2·91 g) in benzene (300 ml) was added during 8 h through a high dilution cycle.[18] After being warmed overnight under reflux the mixture was evaporated, and the residue was recrystallized from hexane–propan-2-ol to give the β-*lactam* (23) (3·40 g, 64%), m.p. 146—147°, $\nu_{max.}$ ($CHCl_3$) 5·69 and 5·76 μm, δ ($CDCl_3$) 2·03 (s, C:CMe) 2·17 (s, C:CMe), and 2·1—2·6 (m, $CH_2{\cdot}CH_2$) (total 10H), 3·53 (s, OMe) and 3·57 (s, OMe) (6H), 6·9—7·5 (13H, complex, Ph), and 7·7—8·0 (2H, m, Ph) (Found: C, 70·3; H, 6·0; N, 2·8; S, 6·1. $C_{31}H_{31}NO_5S$ requires C, 70·3; H, 5·9; N, 2·65; S, 6·0%), *m/e* 529 (M^+) (0·2%), 374 (8). 335 (16), 216 (88), 194 (45), and 165 (100).

Action of Potassium t-Butoxide on 4-(2-*Methoxycarbonylethylthio*)-1-(1-*methoxycarbonyl*-2-*methylprop*-1-*enyl*)-3,3,4-*triphenylazetidin*-2-*one* (23).—(*a*) A solution of compound (23) (317 mg) in dimethoxyethane (4 ml) was added at 0° to a solution of potassium t-butoxide (134 mg) in dimethoxyethane (4 ml). After 2 h at 0° the solvent was removed and the residue was treated with a cold mixture of water and ethyl acetate. The organic layer was washed with 10% sodium hydrogen carbonate, and with water, dried, filtered, and concentrated. Preparative t.l.c. on silica gel (Merck GF_{254}) [elution with hexane–ethyl acetate (3 : 1 v/v)] afforded the thiazolinone (12) (18 mg, 12%), identical (t.l.c. and spectra) with an authentic sample, and the thiazoline (16) (66 mg, 44%).

(*b*) To a solution of compound (23) (1·06 g) in dimethoxyethane (20 ml) a solution of potassium t-butoxide (0·45 g) in dimethoxyethane (20 ml) was added in one portion at 0°. After 20 h at 5° the solvent was evaporated off and a solution of the residue in ethyl acetate was washed successively with cold water, 10% sodium hydrogen carbonate solution, and brine. The organic layer was dried and evaporated and the residue (831 mg) was chromatographed on a silica gel (25 g) column. The composition of the eluant was gradually changed as follows: light petroleum–benzene (4 : 1 v/v) → benzene → benzene–chloroform (4 : 1) → chloroform. The following fractions were successively eluted: (i) the thiazolinone (12) (125 mg, 29%); (ii) methyl diphenylacetate (38 mg, 8%); (iii) an unidentified mixture (248 mg); (iv) the thiazoline (16) (72 mg, 14%). Fractions (i), (ii), and (iv) were identical (t.l.c. and spectra) with authentic samples.

Acidification of the combined aqueous layers followed by extraction with chloroform afforded an uncharacterized mixture (235 mg), the n.m.r. spectrum of which indicated a high phenyl content.

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