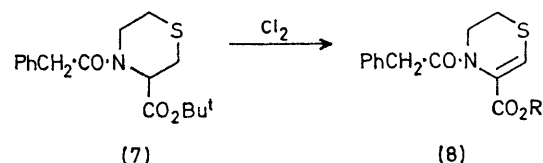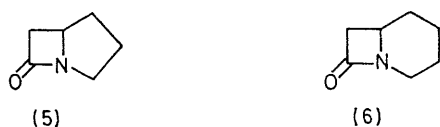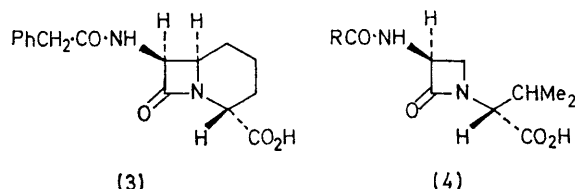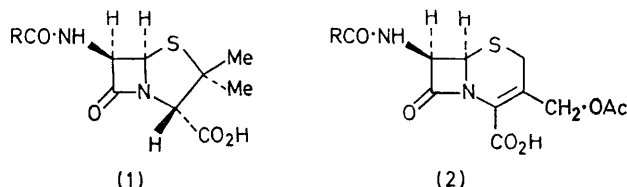# Total Synthesis of Nuclear Analogues of 7-Methylcephalosporin

By David M. Brunwin and Gordon Lowe,* The Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY

A synthetic route which was developed for the preparation of nuclear analogues of the penicillins and cephalosporins has been used to synthesise 8-oxo-7α-phenylacetamido-6αH-1-aza-4-thiabicyclo[4.2.0]octane-2α-carboxylic acid (19), 7α-methyl-8-oxo-7β-phenylacetamido-6αH-1-aza-4-thiabicyclo[4.2.0]octane-2α-carboxylic acid (27), and 7α-methyl-8-oxo-7β-phenylacetamido-6αH-1-aza-4-thiabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (30).

CURRENT hypotheses concerning the mode of action of the penicillins (1) and cephalosporins (2) suggest that the structural features required for antibacterial activity are the acyl-dipeptide system, in the conformation found in these antibiotics, and a reactive β-lactam group.[1] A synthetic route has recently been developed [2,3] which in principle is capable of generating a wide range of nuclear analogues of β-lactam antibiotics possessing these structural features. The nuclear analogue (3) was the first to be prepared by this route but did not show antibacterial properties.[3] Although this analogue possessed the acyl-dipeptide structure, the β-lactam ring was less reactive than that of the penicillins (1) or cephalosporins (2).

dethiopenicillin (4) is an ineffective antibiotic,[4] and by the observation that 1-azabicyclo[3.2.0]heptan-7-one (5) and its derivatives are hydrolysed much more rapidly than 1-azabicyclo[4.2.0]octan-8-one (6) and its derivatives, and indeed are hydrolysed at a rate comparable with that of the penicillins (1).[5] The β-lactam group in the cephalosporins (2) appears to be activated electronically, the enamine grouping together with an allylic acetoxy-group providing a system capable of concerted elimination.[6] The low antibacterial activity of the Δ²-cephalosporins [7] supports this hypothesis, as does X-ray crystallographic evidence.[8]

A key step in the synthetic route which has been developed is the photolysis of a diazo-amide from a cyclic imino-acid ester to give a fused β-lactam–heterocyclic system. Although it is possible to generate the fused β-lactam–thiazolidine ring by this method,[2] the subsequent synthetic manipulation of this highly reactive system presents problems.[9]

The photolysis of diazo-amides leading to β-lactams fused to six-membered nitrogen heterocycles has so far been completely successful,[3,10] and it seemed likely that if a thiomorpholine derivative was used, unsaturation could be introduced into the system at a late stage in the synthesis by way of the thioether. Preliminary studies confirmed that the thiomorpholine derivative (7) when treated with chlorine gave the 5,6-dihydrothiazine ester (8; R = Buᵗ) and the corresponding acid (8; R = H) in a combined yield of 67%.

1,2-Dibromopropionic acid [11] was esterified with isobutene in the presence of sulphuric acid (cf. ref. 12) to give the t-butyl ester (9), which was converted into the t-butyl thiomorpholine-3-carboxylate (10) by treatment with 2-mercaptoethylamine in the presence of triethylamine (cf. ref. 13). The product, which could be conveniently purified by distillation, without the dioxopiperazine being formed, was shown to be the α-imino-ester by formation of a phenylhydantoin with phenyl isocyanate.

Several esters of thiomorpholine-3-carboxylic acid were prepared, including the benzyl and βββ-trichloroethyl compounds, but in view of the problem of hydrogenolysis of benzyl esters in sulphur-containing molecules, the sensitivity to base of βββ-trichloroethyl

The activation of the β-lactam system in the penicillins (1) appears to be due largely if not wholly to the fused thiazolidine ring. This is supported by the fact that

[1] D. J. Tipper and J. L. Strominger, Proc. Nat. Acad. Sci., U.S.A., 1965, 54, 1133; E. M. Wise and J. T. Park, ibid., p. 75.

[2] G. Lowe and J. Parker, Chem. Comm., 1971, 577.

[3] D. M. Brunwin, G. Lowe, and J. Parker, Chem. Comm., 1971, 865; J. Chem. Soc. (C), 1971, 3756.

[4] E. Kaczka and K. Folkers, 'The Chemistry of Penicillin,' eds. H. T. Clark, J. R. Johnson, and R. Robinson, Princeton University Press, 1949, p. 243.

[5] R. H. Earle, D. T. Hurst, and M. Viney, J. Chem. Soc. (C), 1969, 2093; F. Moll, Angew. Chem. Internat. Edn., 1970, 9, 539.

[6] S. H. Eggers, V. V. Kane, and G. Lowe, J. Chem. Soc., 1965, 1262.

[7] J. D. Cocker, S. Eardley, G. I. Gregory, M. E. Hall, and A. G. Long, J. Chem. Soc. (C), 1966, 1142.

[8] R. M. Sweet and L. F. Dahl, J. Amer. Chem. Soc., 1970, 92, 5489.

[9] G. Lowe and D. D. Ridley, unpublished work.

[10] G. Lowe and M. V. J. Ramsay, J.C.S. Perkin I, 1973, 479.

[11] G. Münder and B. Tollens, Annalen, 1873, 167, 222.

[12] A. L. McCloskey, G. S. Fonken, R. W. Kluiber, and W. S. Johnson, Org. Synth., 1954, 34, 26.

[13] B. Belleau, J. Med. Pharm. Soc., 1960, 2, 553.

esters, and the higher yields obtained with the t-butyl ester, this last ester was selected. Since earlier studies had shown the desirability of using a tertiary ester for protecting the malonyl residue for the photolysis reaction,[2] a more acid-labile protecting group than t-butyl was required. Investigation of various 1-aryl-1-methyl-ethyl residues [14] led to the selection of the 1-methyl-1-phenylethyl group.

Ethyl 1-methyl-1-phenylethyl malonate was prepared from ethyl malonyl chloride and 2-phenylpropan-2-ol.[15] The mixed ester was then partially hydrolysed with 1 equiv. of potassium hydroxide in dioxan. The acid was generated from its potassium salt immediately before use, since the free acid catalysed its own de-protection.

1-Methyl-1-phenylethyl hydrogen malonate was coupled with t-butyl thiomorpholine-3-carboxylate by use of dicyclohexylcarbodi-imide to give the required amide (11) in high yield. Diazo exchange with methanesulphonyl azide was catalysed with triethylamine and the reaction mixture was partitioned between water and light petroleum. This simple device provided the pure diazo-compound (12) and the need for purification by chromatography was avoided.

Irradiation of the diazo-compound in a Pyrex vessel for 2 h at room temperature gave a reaction mixture containing both cis- and trans-β-lactam (n.m.r. spectrum). However, attempts to separate these by t.l.c. led to epimerisation of the cis-isomer into trans-isomer. Although epimerisation on silica gel chromatography probably had occurred to some degree in previous syntheses,[3,10] this system was undoubtedly more stereochemically labile. The trans-isomer (13) was conveniently isolated by chromatography of the photo-reaction mixture on neutral alumina, the cis-isomer (14) being rapidly epimerised on the column. When the cis-isomer (14) was required the reaction mixture was treated briefly with dry hydrogen chloride to remove the 1-methyl-1-phenylethyl residue. From the mixture of cis- and trans-acids (estimated by n.m.r. to be in the ratio 7 : 3) the cis-acid (16) was obtained reasonably pure by fractional precipitation. The n.m.r. spectra of both the trans-ester (13) and the cis-acid (16) contained a signal with the characteristic shape for a 2β-proton,[3] thus establishing the stereochemistry across the heterocyclic ring.

Deprotection of the trans-isomer by brief treatment with anhydrous hydrogen chloride gave the acid (15), which was coupled to 1-methyl-1-phenylethylcarbazate with dicyclohexylcarbodi-imide. The protected trans-hydrazide (17) was deprotected by brief treatment with anhydrous hydrogen chloride and the resulting trans-hydrazide was converted into the acid azide with nitrous acid. Rearrangement of the acid azide in refluxing benzene followed by the addition of t-butyl alcohol gave the trans-t-butyl urethane (18). Both t-butyl residues were then removed with trifluoroacetic acid and the product was acylated with phenylacetyl chloride to give 8-oxo-7α-phenylacetamido-6αH-1-aza-4-thiabicyclo-

[4.2.0]octane-2α-carboxylic acid (19), further characterised as its methyl ester.

The essentially pure cis-acid (16) was coupled to 1-methyl-1-phenylethyl carbazate with dicylohexyl-carbodi-imide and the resulting protected cis-hydrazide (20) was converted into the t-butyl urethane by way of the acid azide. However when the Curtius rearrangement was effected in refluxing benzene, it was accompanied by complete epimerisation. When the rearrangement was brought about at room temperature over 3 days and the solution was then treated with t-butyl alcohol at room temperature for 3 days, a mixture of cis- and trans-t-butyl urethanes (21) and (18) was obtained. The overall yield of the cis-isomer (21) was, however, seriously reduced.

In 1965 Tipper and Strominger put forward a hypothesis to account for the mode of action of the penicillins and cephalosporins.[1] They predicted that 6α-methyl-penicillins and 7α-methylcephalosporins might be expected to show enhanced antibacterial activity.[16] The pronounced stereochemical lability of the cis-ester (14) suggested that an alkyl substituent should be readily introduced at this stereochemically labile centre and so form a stereochemically stable system. Since the approach of an alkylating agent to a carbanion generated at this centre would be expected to occur from the least hindered side of the molecule, the required stereoisomer would be formed preferentially. Furthermore the trans-stereoisomer (13) could be usefully employed for this purpose. In the event, when the trans-ester (13) was treated with 1 equiv. of potassium t-butoxide followed by methyl iodide, a single methylated product was isolated. This product was identified as the 7α-methyl derivative (22) on the basis of its exclusive formation and a 17% enhancement of the 6α-H signal in a nuclear Overhauser experiment in which the 7-methyl group was selectively irradiated.

The 7α-methyl derivative (22) was deprotected by brief treatment with anhydrous hydrogen chloride and the acid (23) was coupled to 1-methyl-1-phenylethyl carbazate with dicyclohexylcarbodi-imide. The protected hydrazide (24) was deprotected by brief treatment with anhydrous hydrogen chloride and the resulting acid hydrazide was converted into the acid azide with nitrous acid. Curtius rearrangement of the acid azide was effected in refluxing benzene and the product without isolation was treated with t-butyl alcohol. When the t-butyl urethane (25) ($\nu_{max.}$ 1750 cm^{-1} for the β-lactam) was treated with chlorine at −60° followed by pyridine at room temperature to effect dehydrochlorination, the dihydrothiazine (26) was isolated in good yield. The structure of the product was confirmed by its u.v. [$\lambda_{max.}$ 305 (ε 3700) and 262 nm (ε 4000)] and n.m.r. spectra, and the β-lactam carbonyl i.r. absorption was now at 1800 cm^{-1}. Attempts to remove the t-butyl groups with trifluoroacetic acid, however, led to destruction of the system.

Treatment of the saturated t-butyl urethane (25) with trifluoroacetic acid, followed by acylation with phenyl-

[14] P. Sieber and B. Iselin, Helv. Chim. Acta, 1968, 51, 614, 622.
[15] D. T. Mowry, J. Dazzi, M. Renoll, and R. W. Shortridge, J. Amer. Chem. Soc., 1948, 70, 1916.

[16] J. L. Strominger and D. J. Tipper, Amer. J. Med., 1965, 39, 708.

(9)   (10)

(12)   (11)

(13)   +   (14)

(15)   (16)

(17)   (20)

(18)   (21)
+
(18)

(19)
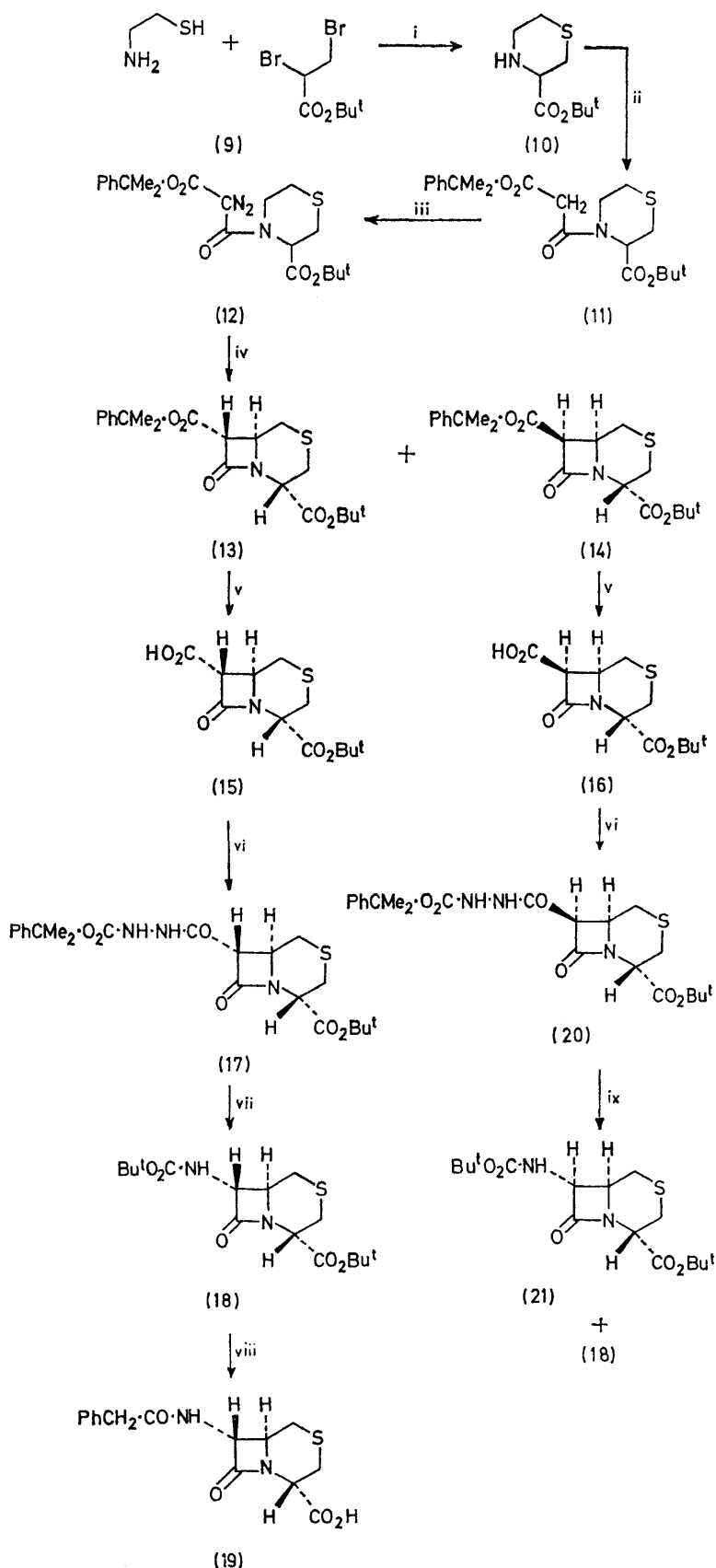
Reagents: i, NEt₃; ii, PhCMe₂·O₂C·CH₂·CO₂H–C₆H₁₁·N=C=N·C₆H₁₁; iii, MeSO₂N₃–NEt₃; iv, *hν* (>300 nm); v, HCl; vi, PhCMe₂·O₂C·NH·NH₂–C₆H₁₁·N=C=N·C₆H₁₁; vii, (*a*) HCl, (*b*) HNO₂, (*c*) heat, (*d*) BuᵗOH; viii, (*a*) CF₃·CO₂H, (*b*) PhCH₂·COCl–NaHCO₃; ix, (*a*) HCl, (*b*) HNO₂, (*c*) spontaneous rearrangement, (*d*) BuᵗOH

acetyl chloride gave 7α-methyl-8-oxo-7β-phenylacetamido-6αH-1-aza-4-thiabicyclo[4.2.0]octane-2α-carboxylic acid (27). Esterification of this acid with βββ-trichloroethyl chloroformate in the presence of triethylamine gave the trichloroethyl ester (28). Treatment of this ester at 0° with 1·1 equiv. of chlorine, followed by dehydrochlorination with pyridine gave the unsaturated

ester (29) as the only isolable product [$\lambda_{max.}$ 306 (ε 5100) and 264 nm (ε 5600); $\nu_{max.}$ 1790 cm^{-1} for the β-lactam]. The βββ-trichloroethyl ester was cleaved with zinc in aqueous acetic to give 7α-methyl-8-oxo-7β-phenylacetamido-6αH-1-aza-4-thiabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (30).

Compounds (19), (27), and (30) were tested at 1 mg ml^{-1} against *Staphalococcus aureus*, *Salmonella typhi*, and *Alcaligines faecalis*, but no antibacterial activity was observed.

The synthesis of methyl 6β-phenylacetamido-6α-methylpenicillanate has been reported recently; the product is ineffective both against *Staphalococcus aureus* 209P on agar plates and *in vivo* in the mouse against *Streptococcus pyogenes*, in which system penicillin G methyl ester is as active as the free acid.[17] 7β-Phenoxyacetamido-deacetoxycephalosporanic acid showed activity only at 1250 μg ml^{-1} against *Staphylococcus aureus* 209P on agar plates, whereas 7β-phenoxyacetamido-deacetoxycephalosporanic acid is active at 15 μg ml^{-1}. These observations indicate that, contrary to the prediction of Strominger and Tipper,[16] a 6α-methyl group in the penicillins and a 7α-methyl group in the cephalosporins seriously impair the antibacterial properties of these systems. The possibility remains therefore that the nuclear analogue (31) may possess useful antibacterial properties.
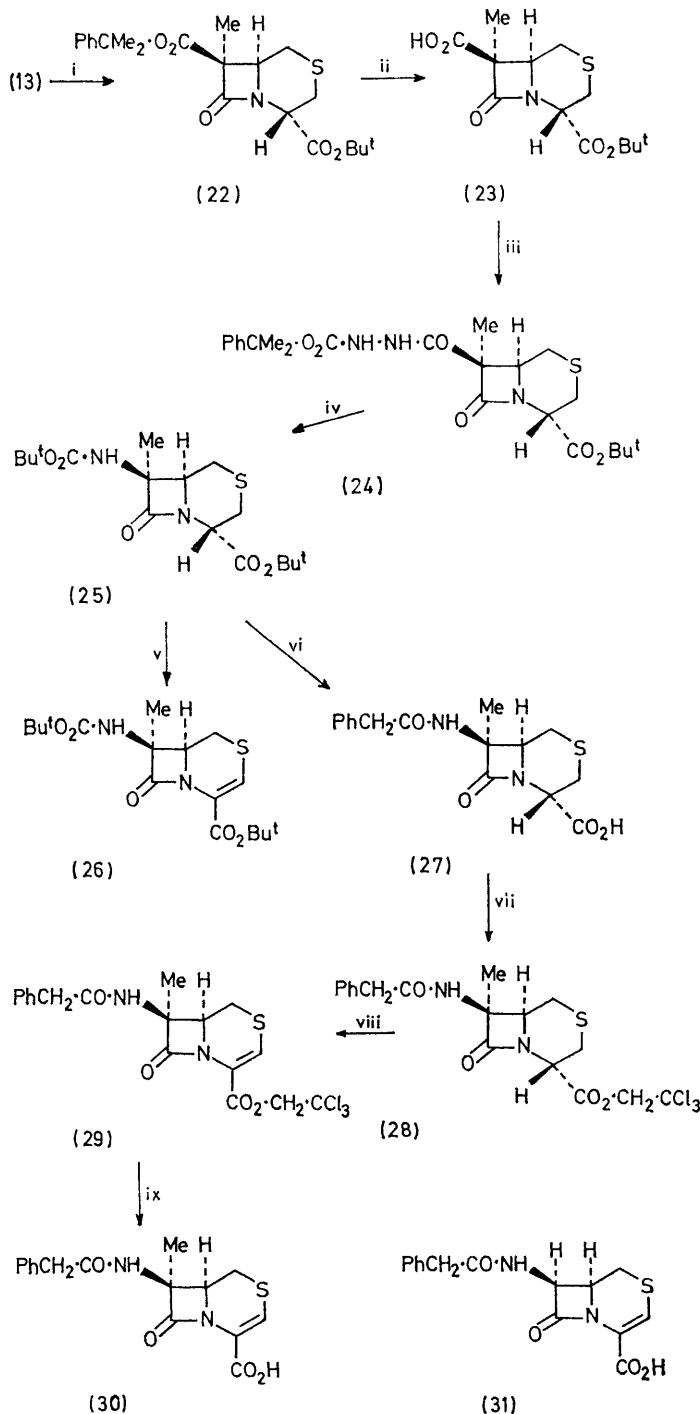
EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. U.v. spectra were determined on a Cary 14 instrument, i.r. spectra on a Perkin-Elmer 257 grating spectrometer, and ¹H n.m.r. spectra on Perkin-Elmer R10 and R14 instruments (operating at 60 and 100 MHz, respectively). The nuclear Overhauser experiment was performed on a Perkin-Elmer R32 instrument operating at 90 MHz with deoxygenated solvent. Mass spectra were determined on A.E.I. MS9 and Varian M.A.T. CH7 instruments. Adsorbents for t.l.c. and preparative layer chromatography (p.l.c.) were HF$_{254+366}$ and PF$_{254+366}$ silica gel (Merck), respectively. Anhydrous sodium sulphate was used to dry organic solutions unless otherwise stated. Light petroleum refers to the fraction b.p. 60—80°. The photoreaction apparatus and procedure are described in a previous paper.[3]

1,2-Dibromopropionic Acid.[11]—To a stirred solution of acrylic acid in chloroform (150 ml) at 0° was added bromine (79·9 g) in portions. The mixture was kept overnight at 20°, and evaporated under reduced pressure. The resultant viscous oil (105 g, 90%) crystallised on cooling and was used without further purification.

t-Butyl 1,2-Dibromopropionate (9).—1,2-Dibromopropionic acid (43 g) dissolved in dry ether (200 ml) was treated with concentrated sulphuric acid (6 ml) and liquefied isobutene (100 ml) in a pressure bottle for 2 days, according to the general method of ref. 12. The bottle was thoroughly cooled in ice–salt before opening, and the mixture was carefully poured into an excess of sodium hydrogen carbonate solution. The ethereal layer was separated and the aqueous layer washed once with ether. The combined ether solutions were washed with brine and dried (Na₂SO₄–K₂CO₃). Removal of the ether gave a pale yellow oil (45 g, 85%), which showed a single spot on t.l.c., R_F 0·6 (70 : 30

Reagents: i, KOBu^t–MeI; ii, HCl; iii, PhCMe₂·O₂C·NH·NH₂–C₆H₁₁·N=C=N·C₆H₁₁; iv, (a) HCl, (b) HNO₂, (c) heat, (d) Bu^{t}OH; v, (a) Cl₂, (b) pyridine; vi, (a) CF₃·CO₂H, (b) PhCH₂·COCl–NaHCO₃; vii, Cl₃C·CH₂·O·COCl–NEt₃; viii, (a) Cl₂, (b) pyridine; ix, Zn–aq.AcOH

17 E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, 1971, **93**, 4324.

light petroleum–ether); $\nu_{max.}$ (CCl$_4$) 1740 cm^{-1} (ester); τ (CCl$_4$) 5·72 (1H, 4 lines, X of ABX, J_{AX} 10, J_{BX} 5 Hz, CHBr), 6·27 (2H, 7 lines, $J_{AB} = J_{AX} = 10$, J_{BX} 5 Hz, CH_2Br), and 8·49 (9H, s, Bu^t).

t-Butyl Thiomorpholine-3-carboxylate (10).—As in the preparation of the corresponding ethyl ester,[13] a mixture of 2-mercaptoethylamine hydrochloride (11·4 g) and triethylamine (10·1 g) in chloroform (60 ml) was added rapidly to a vigorously stirred solution of t-butyl 1,2-dibromopropionate (28·8 g) and triethylamine (20·2 g) in benzene (100 ml). After the initial reaction had subsided (sufficient to cause the solution to reflux for several minutes) the mixture was refluxed for 6 h, washed twice with water and once with brine, dried, and evaporated. The product was distilled using a short Dufton column. An oil (13·0 g, 64%), b.p. 106—108° at 1 mmHg, was collected. T.l.c. showed a major spot at R_F 0·25 and a minor component at R_F 0·35 (70 : 30 ether–light petroleum). The product was used for the next stage without further purification. A sample purified by p.l.c. had $\nu_{max.}$ (CCl$_4$) 3350 (NH) and 1730 cm^{-1} (ester); τ (CCl$_4$) 6·47—7·1 (3H, m, CH·CO$_2$Bu^t and two other ring protons), 7·23—7·68 (4H, m, remaining ring protons), 7·94 (1H, s, removed in D$_2$O, NH), and 8·54 (9H, s, Bu^t).

Equimolar amounts of the crude t-butyl thiomorpholine ester and phenyl isocyanate were heated for 15 min on a boiling water-bath and then boiled with 15% hydrochloric acid for 30 min. A crystalline mass of the phenylhydantoin separated upon cooling and scratching. Recrystallisation from ethanol gave plates, m.p. 123—126° (lit.,[13] 119—120°) (Found: C, 58·15; H, 4·7; N, 11·3; S, 12·6. Calc. for C$_{12}$H$_{12}$N$_2$O$_2$S: C, 58·1; H, 4·85; N, 11·3; S, 12·9%).

t-Butyl N-Phenylacetyl-1,4-thiomorpholine-3-carboxylate (7).—To a stirred solution of the t-butyl thiomorpholine ester (19·3 g) in dichloromethane (250 ml) containing triethylamine (9·6 g) at 5°, phenylacetyl chloride (14·6 g) was added dropwise. The mixture was then stirred for a further 2 h at room temperature and filtered; the filtrate was washed twice with 0·5M-citric acid, saturated sodium hydrogen carbonate solution, and water, dried, and evaporated. The N-*phenylacetyl derivative* (29 g), which crystallised from ether–light petroleum, had m.p. 82—83° (from ether), $\nu_{max.}$ (CCl$_4$) 1735 (ester) and 1655 cm^{-1} (amide) (Found: C, 63·8; H, 7·0; N, 4·5; S, 10·3. C$_{17}$H$_{23}$NO$_3$S requires C, 63·9; H, 6·6; N, 4·4; S, 10·0%).

Reactions of the N-*Phenylacetyl Ester* (7) *with Chlorine* (*with* R. A. FRANICH).—(a) *At* 20°. The thiomorpholine derivative (7) (0·5 g) in dichloromethane (10 ml) was added to a five-fold molar excess of a solution of chlorine in dichloromethane at 20°. The mixture was stirred for 0·5 h, heated on a steam-bath for a further 0·5 h, then evaporated under reduced pressure. The residue was chromatographed on deactivated alumina. Light petroleum–ether (4 : 1) eluted *t-butyl N-[dichloro(phenyl)acetyl]-2,3-dihydro-1,4-thiazine-3-carboxylate* (70 mg, 11%), which crystallised from chloroform–light petroleum as plates, m.p. 97—98°, $\lambda_{max.}$ (EtOH) 279 nm (ε 4300); $\nu_{max.}$ (CHCl$_3$) 1683 (amide) and 1715 cm^{-1} (ester); τ (CDCl$_3$) 8·5 (9H, s, Bu^t), 7·8 (2H, m, S·CH$_2$), 4·7 (1H, t, J 4 Hz, CH·CO$_2$Bu^t), and 2·8 (7H, m, vinyl and aromatic protons) (Found: C, 52·9; H, 5·0; N, 3·6. C$_{17}$H$_{19}$Cl$_2$NO$_3$S requires C, 52·6; H, 5·2; N, 3·6%).

Light petroleum–ether (7 : 3) eluted *t-butyl N-[chloro-(phenyl)acetyl]-5,6-dihydro-1,4-thiazine-3-carboxylate* (200 mg, 37%), which crystallised from chloroform–light petroleum as needles, m.p. 130—132°, $\lambda_{max.}$ (EtOH) 281 nm (ε 7450); $\nu_{max.}$ (CHCl$_3$) 1670 (amide) and 1715 cm^{-1} (ester); τ (CDCl$_3$) 8·5 (9H, s, Bu^t), 7·1 (2H, m, CH$_2$·S), 6·3 (3H, m, CH$_2$·N and PhCH), and 2·8 (6H, m, vinyl and aromatic protons) (Found: C, 57·6; H, 5·7; N, 4·1; S, 9·3. C$_{17}$H$_{20}$ClNO$_3$S requires C, 57·7; H, 5·7; N, 4·0; S, 9·1%).

The eluate obtained with light petroleum–ether (1 : 1) gave a gum (80 mg) shown to be a mixture of acids.

(b) *At* —70°. The thiomorpholine derivative (7) (2·0 g) in dichloromethane (50 ml) was cooled to —70° and treated dropwise with a solution of chlorine (slightly in excess of 1 mol. equiv.) in carbon tetrachloride (5·0 ml) and dichloromethane (5·0 ml). The mixture was stirred at —70° for 1 h, then allowed to warm to 20°. It was then warmed on a steam-bath for 1 h and evaporated under reduced pressure; the residue was chromatographed on p.l.c. plates, with light petroleum–ether (1 : 1) as eluant.

From the least polar band was obtained *t-butyl 5,6-dihydro-N-(phenylacetyl)-1,4-thiazine-3-carboxylate* (8; R = Bu^t) (0·83 g, 41%) as a gum which slowly solidified. Recrystallisation from ether–light petroleum gave needles, m.p. 79—80°, $\lambda_{max.}$ (EtOH) 286 nm (ε 11,300); $\nu_{max.}$ (CHCl$_3$) 1680 (amide) and 1715 cm^{-1} (ester); τ (CDCl$_3$) 8·5 (9H, s, Bu^t), 7·1 (2H, m, CH$_2$·S), 6·3 (2H, s, PhCH_2), 6·1 (2H, m, N·CH$_2$), and 2·8 (6H m, vinyl and aromatic protons) (Found: C, 63·2; H, 7·1; N, 4·3; S, 10·1. C$_{17}$H$_{21}$NO$_3$S requires C, 63·5; H, 7·2; N, 4·4; S, 10·0%).

From the more polar band was obtained *5,6-dihydro-N-(phenylacetyl)-1,4-thiazine-3-carboxylic acid* (8; R = H) (0·46 g, 26%), which crystallised from chloroform–ether as a white powder, m.p. 131—132°, $\nu_{max.}$ (CHCl$_3$) 1680 (amide) and 1690 cm^{-1} (carboxylic acid); τ (CDCl$_3$) 7·1 (2H, m, CH$_2$·S), 6·3 (2H, s, PhCH_2), 6·1 (2H, m, N·CH$_2$), 2·7 (5H, m, aromatic), 2·5 (1H, s, vinyl proton), and 0·6br (s, CO$_2$H, exchangeable with D$_2$O) (Found: C, 59·7; H, 5·0; N, 5·5; S, 12·2. C$_{13}$H$_{13}$NO$_3$S requires C, 59·3; H, 5·0; N, 5·3; S, 12·1%).

Ethyl 1-Methyl-1-phenylethyl Malonate.—Ethyl (chloroformyl)acetate was prepared from ethyl hydrogen malonate and thionyl chloride in the usual way. (In our hands a much superior yield and purer product was obtained than by the method recommended by Breslow *et al.*[18])

The acid chloride (2·01 g) in dry ether (2 ml) was added dropwise to a hot (*ca.* 80°) mixture of 2-phenylpropan-2-ol[15] (2·03 g), dimethylaniline (1·64 g; redistilled from KOH; b.p. 92—94° at 25 mmHg), and dry ether (4 ml). The mixture was then refluxed at 80—90° for 3 h and kept overnight at 20°. The crystalline dimethylaniline hydrochloride was removed by washing twice with water. The ether layer was washed with 10 ml portions of 0·1N-sulphuric acid, then with saturated sodium hydrogen carbonate solution and brine, dried (K$_2$CO$_3$–Na$_2$SO$_4$), and evaporated to give the *diester* as a pale yellow oil (2·65 g, 75%). A sample was purified by chromatography and redistilled for analysis (Found: C, 66·95; H, 7·45. C$_{14}$H$_{18}$O$_4$ requires C, 67·2; H, 7·5%).

1-Methyl-1-phenylethyl Hydrogen Malonate.—The crude ethyl 1-methyl-1-phenylethyl malonate (2·5 g) was dissolved in dioxan (20 ml), AnalaR potassium hydroxide (0·6 g) in water (5 ml) was added, and the mixture was stirred for 3 h at 20° (the final pH was close to 7). More water was added and the mixture was extracted twice with ether. The aqueous layer was filtered to remove a small amount of insoluble material and the water removed under reduced pressure at about 35° to give a white gummy solid. Addition of acetone gave a fine white solid which was collected and washed with acetone and ether (yield 2·2 g, 81%).

[18] D. S. Breslow, E. Baumgarten, and C. R. Hauser, *J. Amer. Chem. Soc.*, 1944, **66**, 1286.

The unpurified potassium salt (2·0 g) was added to a rapidly stirred mixture of ice-cold aqueous citric acid (200 ml; 0·1M) and ethyl acetate (200 ml). After 5 min the layers were separated and the aqueous layer re-extracted with ethyl acetate (100 ml). The combined extracts were washed twice with water and brine, and then dried. Removal of the ethyl acetate below 30° gave the *half ester* as an oil (1·3 g, 80%) which slowly crystallised. Recrystallisation from ether–light petroleum gave plates, m.p. 72—74° (Found: C, 64·8; H, 6·35. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%).

t-Butyl N-(1-Methyl-1-phenylethoxycarbonylacetyl)thio]-*morpholine-3-carboxylate* (11).—The foregoing half ester (6·6 g) was coupled with t-butyl thiomorpholine-3-carb-oxylate (6·1 g) by use of dicyclohexylcarbodi-imide (6·1 g) in dichloromethane (150 ml). After stirring for 3 h at 20°, the solution was diluted with dichloromethane, filtered, and washed with 0·1N-sulphuric acid, sodium hydrogen carbonate solution, and water. After drying and removal of the solvent, the residue (8·05 g, 68%) crystallised. Recrystallisation from ether–light petroleum gave the *thiomorpholine* as needles, m.p. 97—99°, $\nu_{max.}$ (CCl$_4$) 1730 (esters) and 1665 cm^{-1} (amide); τ (CCl$_4$) 2·7 (5H, m, Ph), 4·51br (1H, t, CH·CO$_2$Bu^t), 6·15—7·80 (8H, m, ring protons, including malonyl CH$_2$ at τ 6·65), 8·22 (6H, s, CMe$_2$), and 8·53 (9H, s, Bu^t) (Found: C, 61·8; H, 7·05; N, 3·45. $C_{21}H_{29}NO_5S$ requires C, 61·9; H, 7·15; N, 3·45%).

t-Butyl N-[Diazo-(1-methyl-1-phenylethoxycarbonyl)acetyl]-*thiomorpholine-3-carboxylate* (12).—Compound (11) (8·4 g) was mixed with methanesulphonyl azide[19] (13 g, 5 molar excess) and triethylamine (6·3 ml, 2 molar excess) in acetonitrile (50 ml) and the mixture was kept at 20° for 2 days. The solvent and triethylamine were removed and the residual oil was dissolved in ether and washed with 0·5N-sodium hydroxide and water. The ether was removed and water (50 ml) and light petroleum (50 ml) were added. The mixture was stirred vigorously for a few min and the yellow light petroleum layer was withdrawn and replaced with fresh solvent. This process was repeated several times, a small amount of gum insoluble in both water and light petroleum being discarded. The combined light petroleum layers were washed thrice with water and dried. Removal of the solvent gave a pale yellow gum, which t.l.c. and spectral evidence showed to be the pure diazo-com-pound (8·7 g, 95%), $\lambda_{max.}$ (EtOH) 257 nm (ε 10,000); $\nu_{max.}$ (CCl$_4$) 2150 (CN$_2$), 1735, 1705 (esters), and 1630 cm^{-1} (amide); τ (CCl$_4$) 2·67 (5H, m, Ph), 5·12br (1H, t, CH·CO$_2$Bu^t), 6·1—7·9 (6H, m, ring protons), 8·18 (6H, s, CMe$_2$), and 8·53 (9H, s, Bu^t).

Irradiation of the Diazo-ester (12).—(a) *To produce the maximum yield of* trans-β-*lactam* (13).—The diazo-com-pound (2·0 g) dissolved in dry benzene (200 ml) was irradiated for 2 h at room temperature. The solvent was removed and the residue chromatographed on neutral alumina (deactivated to grade 5) with light petroleum–ether. Light petroleum eluted unchanged diazo-derivative. Ether–light petroleum (1 : 3) eluted *t-butyl* 7α-(1-methyl-1-*phenylethoxycarbonyl)-6αH-1-aza-4-thiabicyclo*[4.2.0]*octane-2α-carboxylate* (13), which crystallised from ether–light petroleum (40% overall yield) as needles, m.p. 107—108° (with a phase change at 80—82°), $\nu_{max.}$ (CCl$_4$) 1770 (β-lactam) and 1730 cm^{-1} (ester); τ (CCl$_4$) 2·56 (5H, m, Ph), 5·47 (1H, m, H-2β), 5·95 (1H, $J_{5,6}$ 5 and 11, $J_{6,7\beta}$ 2 Hz, H-6), 6·38 (1H, d, $J_{6,7\beta}$ 2 Hz, H-7β), 7·0—7·6 (4H, m, remaining ring protons), 8·16 and 8·21 (each 3H, s, CMe$_2$), and 8·55 (9H, s, Bu^t); τ (C$_6$H$_6$) 5·63 (1H, m, H-2β) and 8·23 and 8·27 (each

3H, s, CMe$_2$) (Found: C, 62·1; H, 6·7; N, 3·3. $C_{21}H_{27}NO_5S$ requires C, 62·2; H, 6·65; N, 3·45%).

(b) *To produce the maximum yield of* cis-β-*lactam* (16). The diazo-compound (2 g) was irradiated in dry benzene (200 ml) for 2 h at room temperature and the solvent was removed under reduced pressure. The residue was dis-solved in dichloromethane (15 ml) and cooled to 0°. Dry hydrogen chloride was passed through the solution in a vigorous stream for 3 min. Solvent and excess of hydrogen chloride were removed under reduced pressure, the residue was dissolved in ether (12 ml), and light petroleum (25 ml) was slowly added, precipitating an off-white solid. The mixture was kept at 0° for 1 h and the solid was collected and washed with light petroleum. The n.m.r. spectrum of the product indicated an essentially uncontaminated mixture (0·8 g) of *cis-* and *trans-β-lactam* acids (15) and (16), in the ratio 7 : 3. Fractional precipitation occurred if the cooling step was omitted, the more soluble *trans*-compound remain-ing in solution. The almost pure *cis*-acid (16) (0·5 g) was obtained in this way: τ [(D$_3$C)$_2$SO] 1·65 (1H, s, CO$_2$H), 5·3br (1H, t, H-2β), 5·68 (1H, d, $J_{6,7\alpha}$ 4·8 Hz, H-7α), 6·0 (1H, m, H-6), 7·0—7·4 (4H, m, ring proton), and 8·53 (9H, s, Bu^t). The product was used without further purification for subsequent reactions.

t-Butyl 7β-[3-(1-Methyl-1-phenylethoxycarbonyl)carbazoyl]-*8-oxo-6αH-1-aza-4-thiabicyclo*[4.2.0]*octane-2α-carboxylate* (20).—The *cis*-acid (16) (0·1 g) was coupled to 1-methyl-1-phenylethyl carbazate[14] (0·068 g) with dicyclohexyl-carbodi-imide (0·071 g) in dichloromethane (5 ml), with stirring at 0° for 30 min and for 3 h at 20°. The mixture was worked up in the usual way to give the *hydrazide* (20) (0·139 g) as a white foam. A sample was purified by p.l.c. Three elutions with chloroform (final R_F 0·1) gave a gum which was precipitated as a white amorphous solid from ether–light petroleum, $\nu_{max.}$ (CHCl$_3$) 3420, 3300 (NH), 1750 (β-lactam), 1740 (ester), 1700 (urethane), and 1690 cm^{-1} (hydrazide); τ (CDCl$_3$) 1·77br (1H, s, NH), 2·59br (5H, s, Ph), 3·17br (1H, s, NH), 5·38 (1H, m, H-2β), 5·65—5·95 (2H, m, H-6 and H-7α), 7·0—7·7 (4H, m, remaining ring protons), 8·20 (6H, s, CMe$_2$), and 8·50 (9H, s, Bu^t). In benzene, solvent shifts separated the H-6 and H-7α signals giving the H-7α signal as d, $J_{6,7\alpha}$ 5 Hz (Found: C, 57·2; H, 6·29; N, 9·0. $C_{22}H_{29}N_3O_6S$ requires C, 57·0; H, 6·25; N, 9·05%).

t-Butyl 7α-[3-(1-Methyl-1-phenylethoxycarbonyl)carbazoyl]-*8-oxo-6αH-1-aza-4-thiabicyclo*[4.2.0]*octane-2α-carboxylate* (17).—The *trans-β-lactam* (13) was treated with dry hydrogen chloride in dichloromethane solution at 0° as described previously, to give, on work-up, the *trans*-acid (15), τ (CDCl$_3$) 6·15 (1H, d, $J_{6,7\alpha}$ 2 Hz, H-7β).

The *trans*-acid (0·1 g) was converted into the *hydrazide* (17) as just described, giving an amorphous solid (0·12 g) (lower R_F in CHCl$_3$ than the 7β-isomer) after p.l.c.; i.r. spectrum similar to that of the 7β-isomer; τ (CDCl$_3$) 1·7br (1H, s, NH), 2·6 (5H, s, Ph), 3·06br (1H, s, NH), 5·38 (1H, m, H-2β), 5·77 (1H, 8 lines, H-6), 6·28 (1H, d, J 2 Hz, H-7β), 6·95—7·7 (4H, m, remaining ring protons), 8·20 (6H, s, CMe$_2$), and 8·50 (9H, s, Bu^t) (Found: C, 57·1; H, 6·4; N, 8·8. $C_{22}H_{29}N_3O_6S$ requires C, 57·0; H, 6·25; N, 9·05%).

t-Butyl 8-Oxo-7α-t-butoxycarbonylamino-1-aza-4-thiabi-*cyclo*[4.2.0]*octane-2α-carboxylate* (18).—The hydrazide (17) (0·20 g) was deprotoned with dry hydrogen chloride in dichloromethane at 0° for 3 min. The solvent was removed under reduced pressure, the product was dissolved in cold

[19] M. T. Reagan and A. Nickon, *J. Amer. Chem. Soc.*, 1968, **90**, 4096.

10% hydrochloric acid (5 ml), and the vigorously stirred solution was treated with solid sodium nitrite (*ca.* 0·3 g) at 0° for 5 min. The acid azide was extracted with dichloromethane and the solution washed with water, dried, and evaporated. Immediately the acid azide was dissolved in dry benzene (10 ml) and refluxed for 45 min. t-Butyl alcohol (5 ml) was added and refluxing was continued for a further 1 h. The crude mixture was purified by p.l.c. Two elutions with ether–light petroleum (7 : 3) gave a band with R_F 0·25 (first elution). This gave the *7α-t-butyl urethane* (0·05 g, 27% over the four reactions), which crystallised from benzene–light petroleum as an off-white solid. Recrystallisation from the same solvent gave plates, m.p. 145—153°, $\nu_{max.}$ (CCl$_4$) 3450 (NH), 1765 (β-lactam), and 1735 cm^{-1} (ester); τ (CCl$_4$) 3·86 (1H, d, $J_{NH,7\beta}$ 8 Hz, NH), 5·49 (2H, m, H-7β and H-2β), 6·27 (1H, m, H-6), 6·95—7·45 (4H, m, ring protons), and 8·48 and 8·55 (9H, each, 2 × Bu^{t}O); τ (C$_6$H$_6$) 5·38br (1H, d, $J_{NH,7\beta}$ 8 Hz, H-7β), 5·53br (1H, d, H-2β), and 6·23 (1H, 8 lines, $J_{6,7\beta}$ 1·9 Hz, H-6), *m/e* 358·1569 (*M*$^+$) (C$_{16}$H$_{26}$N$_2$O$_5$S requires *M*, 358·1562).

8-Oxo-7α-phenylacetamido-6αH-1-aza-4-thiabicyclo[4.2.0]-octane-2α-carboxylic Acid (19).—The t-butyl urethane (18) (0·04 g) was treated with anhydrous trifluoroacetic acid for 1 h at 20°; the acid was then removed under reduced pressure. The residual gum was dissolved in 30% aqueous acetone (1 ml; reagent grade) and solid sodium hydrogen carbonate (0·04 g, 4 equiv.) was added, followed by phenylacetyl chloride (0·019 g, 1·1 equiv.) dissolved in a small volume of acetone. The mixture was stirred and cooled to 0° for 1 h. The acetone was removed under reduced pressure, water (3 ml) was added, and the solution was extracted with ether. The aqueous solution was cooled, acidified to pH 2 with 2N-sulphuric acid, and immediately extracted thrice with chloroform. The extract was dried and evaporated. The residual *7α-phenylacetamido-derivative* (19) (0·028 g) soon solidified. After two attempted recrystallisations from acetone–ether the white amorphous solid had m.p. 125—140° (Found: C, 56·3; H, 5·3; N, 8·35. C$_{15}$H$_{16}$N$_2$O$_4$S requires C, 56·35; H, 5·0; N, 8·75%).

A sample was treated with diazomethane to give the methyl ester, $\nu_{max.}$ (CHCl$_3$) 3400 (NH), 1765 (β-lactam), 1750 (ester), and 1685 cm^{-1} (amide); τ (CDCl$_3$) 2·6 (s, with CHCl$_3$, Ph), 5·03 (1H, m, H-7β), 5·2 (1H, m, H-2β), 6·15 (3H, s, OMe), and 6·25—6·4 (m, H-6 and PhCH$_2$·CO at τ 6·33); *m/e* 344 (*M*$^+$) (C$_{16}$H$_{18}$N$_2$O$_4$S requires *M*, 344).

t-Butyl 8-Oxo-7β-t-butoxycarbonylamino-6αH-1-aza-4-thiabicyclo[4.2.0]octane-2α-carboxylate (21).—The essentially pure hydrazide (20) (0·15 g) was converted into the 7β-acid azide as described for the 7α-derivative. Subsequent Curtius rearrangement and conversion of the isocyanate into the 7β-t-butyl urethane was accompanied by complete epimerisation from the 7β- to the 7α-configuration. However, rearrangement at 20° for 72 h in dry benzene (5 ml), followed by reaction with dry t-butyl alcohol (2·5 ml) for a further 72 h gave a mixture of 7β- and 7α-t-butyl urethanes. P.l.c. (one elution with ether–light petroleum, 7 : 3) gave the 7β-t-butyl urethane (21), R_F 0·45, as a white solid (0·005 g), and the 7α-t-butyl urethane (18), R_F 0·25 as a gum (0·005 g). Their i.r. spectra were essentially identical, and the n.m.r. spectrum of the product with R_F 0·25 was identical with that of authentic 7α-t-butyl urethane (18). The 7β-t-butyl urethane (21) had τ (CDCl$_3$) 5·12 (1H, q, $J_{6,7\alpha}$ 5 Hz, $J_{7\alpha,NH}$ 7 Hz, H-7α), 5·42br (1H, t, H-2β), 5·95 (1H, 5 lines, $J_{6,7\alpha}$ 5 Hz, $J_{5,6}$ 5 and 10 Hz, H-6), 7·05—7·5 (4H, 2 multiplets, ring protons), and 8·5 and 8·55 (9H each, 2 × OBu^t); *m/e* 358 (*M*$^+$) (C$_{16}$H$_{26}$N$_2$O$_5$S requires *M*, 358).

t-Butyl 7α-Methyl-7β-(1-methyl-1-phenylethoxycarbonyl)-8-oxo-6αH-1-aza-4-thiabicyclo[4.2.0]octane-2α-carboxylate (22). —The *trans*-β-lactam (13) (0·085 g) was dissolved in dry ether (2 ml) and cooled to 0°. A solution of potassium t-butoxide (1 equiv.) in t-butyl alcohol was added with stirring, followed after 2 min by methyl iodide (0·3 ml). The mixture was stirred at 20° for 20 h, diluted with ether, washed twice with water, dried, and evaporated. From the resulting gum (0·075 g) (homogeneous by t.l.c.) an off-white solid was obtained by cooling and scratching under light petroleum. Recrystallisation from light petroleum–ether gave the *7α-methyl derivative* (22) as needles, m.p. 100—102°, $\nu_{max.}$ (CCl$_4$) 1765 (β-lactam) and 1730 cm^{-1} (ester); τ (CCl$_4$) 2·72 (5H, m, Ph), 5·50br (1H, t, H-2β), 6·35 (1H, q, $J_{5,6}$ 5 and 11 Hz, H-6), 7·05—7·60 (4H, m, C-3 and C-5 protons), 8·17 and 8·19 (3H each, s, CMe$_2$), 8·43 (3H, s, 7-CH$_3$), and 8·51 (9H, s, Bu^t); irradiation at τ 8·43 gave a 17% nuclear Overhauser enhancement of the signal at τ 6·35; τ (C$_6$H$_6$) 5·63br (1H, d, $J_{2\beta,3}$ 5 and 2 Hz, H-2β), 6·38 (1H, q, $J_{5,6}$ 4 and 12 Hz, H-6), 7·23 (1H, t, $J_{5\beta,6}$ 12, $J_{5\beta,5\alpha}$ 12 Hz, H-5β), 7·53 (2H, AB of ABX system, $J_{3\alpha,3\beta}$ 14, $J_{2,3}$ 5 and 2 Hz, C-3 protons), 7·88 (1H, dd, $J_{5\alpha,5\beta}$ 12, $J_{5\alpha,6}$ 4 Hz, H-5α), 8·3 and 8·35 (3H, each, s, CMe$_2$), 8·43 (3H, s, CH$_3$), and 8·72 (9H, s, Bu^t) (Found: C, 63·1; H, 7·05; N, 3·45. C$_{22}$H$_{29}$NO$_5$S requires C, 63·0; H, 6·9; N, 3·35%).

7α-Methyl-8-oxo-2α-t-butoxycarbonyl-6αH-1-aza-4-thiabicyclo[4.2.0]octane-7β-carboxylic Acid (23).—In a repeat of the foregoing preparation, starting with the lactam (13) (0·16 g), the resultant 7α-methyl derivative (0·18 g) was dissolved in dichloromethane (2 ml) and cooled to 0°. Dry hydrogen chloride was passed through the solution for 3 min in a vigorous stream and then removed under reduced pressure. Trituration of the remaining gum with light petroleum containing a little ether gave a white solid. Recrystallisation could not be achieved, but the solid (0·076 g, 65% over the two stages) decarboxylated at *ca.* 150°; $\nu_{max.}$ (CHCl$_3$) 3000br, 1760 (β-lactam), and 1735 with shoulder at 1730 cm^{-1} (ester and acid); τ (CDCl$_3$) 1·15 (*ca.* 1H, s, CO$_2$H), 5·35br (1H, t, H-2β), 6·17 (1H, q, $J_{5,6}$ 4·5 and 10·5 Hz, H-6), 6·9—7·5 (4H, m, C-3 and C-5 protons), 8·35 (3H, s, CH$_3$), and 8·50 (9H, s, Bu^t); τ (C$_6$H$_6$) 8·34 (3H, s, CH$_3$) and 8·7 (9H, s, Bu^t). The product was essentially pure, and was used without further purification.

t-Butyl 7α-Methyl-7β-[3-(1-methyl-1-phenylethoxycarbonyl)carbazoyl]-8-oxo-6αH-1-aza-4-thiabicyclo[4.2.0]octane-2α-carboxylate (24).—The 7β-carboxylic acid (23) (0·105 g) was dissolved in dichloromethane (5 ml) and cooled to 0°. 1-Methyl-1-phenylethyl carbazate (0·068 g) and dicyclohexylcarbodi-imide (0·071 g) were added; the mixture was stirred at 0° for 30 min and for 6 h at 20°, then filtered. The residue was washed with dichloromethane and the combined filtrates were washed with 2N-sulphuric acid, saturated sodium hydrogen carbonate solution, and water, dried, and evaporated. The residual white foam (0·155 g, 97%) was virtually pure hydrazide (24), τ (CDCl$_3$) 1·85br and 3·35br (1H each, s, NH·NH), 2·60 (5H, s, Ph), 5·4 (1H, dd, $J_{2\beta,3}$ 2 and 5 Hz, H-2β), 6·2 (1H, q, $J_{5,6}$ 4 and 11 Hz, H-6), 7·0—7·5 (4H, m, C-3 and C-5 protons), 8·2 (6H, s, CMe$_2$), 8·32 (3H, s, CH$_3$), and 8·5 (9H, s, Bu^t).

t-Butyl 7α-Methyl-8-oxo-7β-t-butoxycarbonylamino-6αH-1-aza-4-thiabicyclo[4.2.0]octane-2α-carboxylate (25).—The 7β-hydrazide (24) (0·6 g) was dissolved in dichloromethane (10 ml) and cooled to −5°. Dry hydrogen chloride was bubbled through the solution for 10 min and the solvent was then removed under reduced pressure. The residual

gum was dissolved in 10% hydrochloric acid (10 ml; previously cooled to 0°) and extracted once with ether. The aqueous acid layer was stirred at 0° and excess of solid sodium nitrite was added, followed by dichloromethane (20 ml). After 5 min at 0°, the dichloromethane layer was separated and the aqueous layer extracted with dichloromethane. The combined organic layers were dried and evaporated. The residual gum was taken up in anhydrous benzene; the solution was filtered and dried (for 2 h) over a molecular sieve. The benzene solution was refluxed in thoroughly dry apparatus for 45 min. Dry t-butyl alcohol (5 ml) was added and refluxing was continued for a further 3 h. P.l.c. of the product (elution with ether–light petroleum, 7 : 3) gave a gum which crystallised spontaneously. Recrystallisation from ether gave the 7β-*t*-butyl *urethane* as needles (0·06 g), m.p. 189—191°, $\nu_{max.}$ (CHCl$_3$) 1750 (β-lactam), 1720 (ester), and 1700 cm^{-1} (urethane); τ (CDCl$_3$) 5·05br (1H, s, NH), 5·4br (1H, t, H-2β), 6·17 (1H, q, $J_{5,6}$ 6 and 10 Hz, H-6), 7·05—7·35 (4H, m, C-3 and C-5 protons), 8·45 (3H, s, CH$_3$), and 8·5 and 8·57 (9H each, s, 2 × OBu^t) (Found: C, 54·85; H, 7·65; N, 7·3. C$_{17}$H$_{28}$N$_2$O$_5$S requires C, 54·8; H, 7·55; N, 7·55%).

t-Butyl 7α-*Methyl*-8-*oxo*-7β-*t-butoxycarbonylamino*-6α*H*-1-*aza*-4-*thiabicyclo*[4.2.0]*oct*-2-*ene*-2-*carboxylate* (26).—The 7β-urethane (25) (0·02 g) was dissolved in dichloromethane (2 ml) and cooled to −60°. A solution of chlorine (5 equiv.) in carbon tetrachloride diluted with dichloromethane (5 ml) was added in one portion. After 1 h the mixture was allowed to warm to 20° and evaporated under reduced pressure. Pyridine (0·012 g) in dichloromethane (2 ml) was added to the residual gum and the mixture was left at 20° overnight. After removal of solvent and the excess of pyridine, p.l.c. (one elution with ether; R_F 0·1) gave a foam (0·012 g, 60%) of the pure *dihydro-1,4-thiazine* (26), $\lambda_{max.}$ (EtOH) 262 (ε 4000) and 305 nm (ε 3700); $\nu_{max.}$ (CHCl$_3$) 1800 (β-lactam), 1725 (ester), 1710 (urethane), and 1610 cm^{-1} (double bond); τ (CDCl$_3$) 3·47 (1H, s, H-3), 5·03br (1H, s, NH), 6·07 (2H, m, $J_{5\alpha,5\beta}$ 13, $J_{5\alpha,6}$ 3, $J_{5\beta,6}$ 13 Hz, H-5α, H-6), 6·95 (1H, t, $J_{5\alpha,5\beta}$ 13, $J_{5\beta,6}$ 13 Hz, H-5β), 8·37 (3H, s, CH$_3$), and 8·47 and 8·57 (9H each, s, 2 × OBu^t).

7α-*Methyl*-8-*oxo*-7β-*phenylacetamido*-6α*H*-1-*aza*-4-*thiabicyclo*[4.2.0]*octane*-2α-*carboxylic Acid* (27).—The 7β-t-butyl urethane (25) (0·07 g) was dissolved in dichloromethane (0·7 ml) and treated with anhydrous trifluoroacetic acid (0·7 ml) for 90 min at 20°. The solvent and trifluoroacetic acid were removed under reduced pressure and the residue was taken up in water (1 ml). Solid sodium hydrogen carbonate was added until the pH of the solution was between 8 and 9. The mixture was cooled to 0° and stirred vigorously while phenylacetyl chloride (0·028 g, 1·1 equiv.), dissolved in reagent grade acetone (0·5 ml), was added dropwise over 10 min, with alternate additions of solid sodium hydrogen carbonate, so that pH 8—9 was maintained. The mixture was stirred for a further 45 min at 0° and the acetone was removed under reduced pressure. Water (5 ml) was added, and the solution was extracted once with ether. The aqueous solution was cooled, acidified to pH 2 with 2N-sulphuric acid, and immediately extracted thrice with chloroform. The extract was dried and the solvent removed. The residual white solid (0·052 g, 82%) crystallised from chloroform–light petroleum to give the 7β-*phenylacetamido-derivative* (27) as needles, m.p. 131—136°, $\nu_{max.}$ (CHCl$_3$) 1750 (β-lactam), 1720 (acid), and 1680 cm^{-1} (amide) (Found: C, 57·9; H, 5·7; N, 8·2. C$_{16}$H$_{18}$N$_2$O$_4$S requires C, 57·5; H, 5·4; N, 8·3%).

βββ-*Trichloroethyl* 7α-*Methyl*-8-*oxo*-7β-*phenylacetamido*-6α*H*-1-*aza*-4-*thiabicyclo*[4.2.0]*octane*-2α-*carboxylate* (28).—The 7β-phenylacetamido-carboxylic acid (27) (0·045 g) was dissolved in dichloromethane containing 0·1% water (1 ml) and stirred at 0° with triethylamine (0·0135 g). βββ-Trichloroethyl chloroformate (0·0425 g) was added in one portion, followed 2 min later by pyridine (0·02 ml). After 5 min, excess of 2% sulphuric acid was added and the organic layer was separated, washed with saturated sodium hydrogen carbonate solution and water, and dried. The solvent was removed under reduced pressure; the residual gum (0·045 g, 71%) was essentially pure βββ-trichloroethyl ester (28), R_F 0·35 (ether), $\nu_{max.}$ (CH$_2$Cl$_2$) 1757 (β-lactam and trichloroethyl ester) and 1685 cm^{-1} (amide).

βββ-*Trichloroethyl* 7α-*Methyl*-8-*oxo*-7β-*phenylacetamido*-6α*H*-1-*aza*-4-*thiabicyclo*[4.2.0]*oct*-2-*ene*-2-*carboxylate* (29).—The βββ-trichloroethyl ester (28) (0·021 g) was dissolved in dichloromethane (3 ml) and cooled to 0° in a flask sealed with a serum cap. A solution of chlorine in carbon tetrachloride at 0° (0·33 ml; containing 1·1 eqiuv. of chlorine) was added in one portion by syringe. After stirring for 30 min at 0° and for a further 30 min at 20° the solvent and the excess of chlorine were removed under reduced pressure. The residue was taken up in dichloromethane (2 ml) and pyridine (0·009 g) was added. After 2 h at 20°, the solvent and pyridine were removed. P.l.c. on one silica gel plate (20 × 20 × 0·1 mm) gave an intense dark blue (254 nm) band close to the base-line (two elutions with CHCl$_3$). The product was washed off with reagent grade ethyl acetate (500 ml) and chloroform (100 ml). The pale yellow gum (0·005 g, 25%) gave the product (29) as a white solid when triturated with ether; $\lambda_{max.}$ (EtOH) 264 (ε 5600) and 306 nm (5100); $\nu_{max.}$ (CHCl$_3$) 1790 (β-lactam), 1750 (ester), 1680 (amide), and 1605 cm^{-1} (double bond); τ 2·75 (5H, s, Ph), 3·25 (1H, s, =CH), 4·1 (1H, s, NH), 5·12 (2H, AB, J 12 Hz, O·CH$_2$·CCl$_3$), 5·61 (1H, dd, $J_{5\alpha,5\beta}$ 13, $J_{5\alpha,6}$ 3 Hz, H-5α), 5·91 (1H, dd, $J_{5\beta,6}$ 13, $J_{5\alpha,6}$ 3 Hz, H-6), 6·42 (2H, s, PhCH$_2$·CO), 7·05 (1H, t, $J_{5\alpha,5\beta}$ 13, $J_{5\beta,6}$ 13 Hz, H-5β), and 8·27 (3H, s, CH$_3$); m/e 462 (*M*$^+$), 434 (*M*$^+$ − CO), 343 (*M*$^+$ − PhCH$_2$·CO), 315 (*M*$^+$ − O·CH$_2$·CCl$_3$), and 274 (*M*$^+$ − PhCH$_2$·CO·NH−CMe=C=O). All these peaks except that at 315 had the characteristic satellites at m/e +2 and +4 resulting from chlorine isotopes (C$_{18}$H$_{17}$Cl$_3$N$_2$O$_4$S requires *M*, 462).

7α-*Methyl*-8-*oxo*-7β-*phenylacetamido*-6α*H*-1-*aza*-4-*thiabicyclo*[4.2.0]*oct*-2-*ene*-2-*carboxylic Acid* (30).—The unsaturated βββ-trichloroethyl ester (29) (0·005 g) was dissolved in 90% (v/v) aqueous acetic acid and freshly activated zinc (0·03 g) was added in small portions over 30 min with vigorous stirring at 20°. After stirring for a further 2 h, the zinc was removed and the acetic acid in the filtrate was evaporated off under reduced pressure at 20°. The residue was dissolved in water, the pH adjusted to 2, and the solution extracted three times with chloroform. The chloroform layer was dried and evaporated below 20° to give the unsaturated acid (30) (0·0015 g, 42%), $\lambda_{max.}$ (EtOH) 296 nm (ε 4300); $\nu_{max.}$ (CHCl$_3$) 1775 (β-lactam), 1725 (acid), 1680 (amide), and 1600 cm^{-1} (double bond).