Studies Related to Penicillins. Part VIII.[1] The Rearrangement of Penicillanic Acid Derivatives to 1,3-Thiazines [2]

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A mixture of methoxymethyl 6α-phthalimidopenicillanate (7) and 2-(3,6-dihydro-6-oxo-5-phthalimido-2*H*-1,3-thiazin-3-yl)-3-methylbut-2-enoic acid (17) is formed in the reaction of methoxymethyl 6β-phthalimidopenicillanate (1) with triethylamine. Methoxymethyl (3*S*)-2,3,4,7-tetrahydro-2,2-dimethyl-7-oxo-6-phthalimido-1,4-thiazepine-3-carboxylate (10) is shown to be a likely precursor of the acid (17). Methoxymethyl 6β-*p*-nitrobenzylideneaminopenicillanate (5) undergoes an analogous rearrangement under similar conditions.

The methyl ester (16) of the acid (17) is converted into the racemate of methyl (*E*)-β-[4(*S*)-methoxycarbonyl-5,5-dimethylthiazolidin-3-yl]-α-phthalimidoacrylate (22) in the presence of methanolic sodium methoxide. Iodine catalyses the isomerisation of the latter derivative to the racemate of the thermodynamically favoured (*Z*)-isomer (23), which may be prepared by diazomethane esterification of the acid derived from 4(*S*)-5,5-dimethylthiazolidine-4-carboxylic acid and methyl α-phthalimidomalonaldehydate.

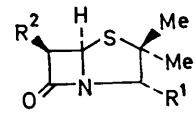
THE epimerisation of penicillanic acid derivatives at position 6 has received considerable recent attention.[1,3-5] It occurs when a diacylamino-, an acylalkylamino-, a trialkylammonium, or an arylmethyleneamino-substituent is present at position 6 and the process is usually base-catalysed.

In the presence of a strong base such as 1,5-diazabicyclo[4,3,0]non-5-ene (DBN), 6β-substituted penicillanic acid derivatives rapidly equilibrate with the 6α-isomers. The equilibrium constant is sensitive to the steric requirement of the 6-substituent:[5] thus, with the phthalimido-group the 6α-derivative is dramatically favoured [>99% in the case of compound (1)] while with an arylmethyleneamino-group, *e.g.* [compound (4)], the 6β-isomer can comprise up to 47% of the equilibrium mixture.

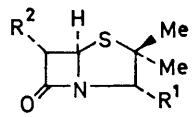
When a weak base is employed, the epimerisation process is accompanied by a rearrangement in which a 1,4-thiazepine is formed. Thus, Kovacs *et al.*[6] isolated compound (11) (25%) in addition to the epimer (8) (*ca.* 50%) from the reaction of methyl 6β-phthalimidopenicillanate (2) with triethylamine. Under similar conditions the homopenicillanate (3) yielded [4] a mixture of the thiazepine (13) (32%) and the epimer (9) (40%). These reactions are essentially irreversible and there is little tendency for the 6α-derivatives to be transformed into the 1,4-thiazepines under the reaction conditions.

The reaction of methoxymethyl 6β-phthalimidopenicillanate [1] (1) with triethylamine has now been investigated. In contrast to the behaviour of the esters (2) and (3), it afforded a single neutral product (25%). The product, which was stable under the reaction conditions, was identical to the derivative obtained from the reaction of the ester (1) with DBN and, therefore, is methoxymethyl 6α-phthalimidopenicillanate [1] (7). No material corresponding to the thiazepine (10) was detected although an amorphous acid was isolated in 63% yield. The acid afforded a crystalline methyl ester which, on the basis of mass spectroscopy, possessed the molecular formula, $C_{18}H_{16}N_2O_5S$; consequently, the acid is derived from compound (1) by the loss of methanol. The ester, which was optically inactive, is formulated as the methyl thiazinylbutenoate (16) on the basis of spectroscopic evidence and, therefore, the acid possesses structure (17).

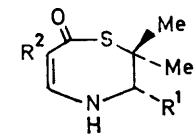
In order to provide some chemical support for its structure, the reaction of the ester (16) with methanolic



(1) $R^1 = CO_2{\cdot}CH_2{\cdot}OMe$, R^2 = phthalimido
(2) $R^1 = CO_2Me$, R^2 = phthalimido
(3) $R^1 = CH_2{\cdot}CO_2Me$, R^2 = phthalimido
(4) $R^1 = CO_2{\cdot}CH_2{\cdot}OMe$, R^2 = 2-hydroxy-1-naphthylmethyleneamino
(5) $R^1 = CO_2{\cdot}CH_2{\cdot}OMe$, R^2 = *p*-nitrobenzylideneamino
(6) $R^1 = CO_2Me$, R^2 = *p*-nitrobenzylideneamino



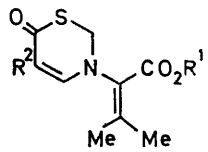
(7) $R^1 = CO_2{\cdot}CH_2{\cdot}OMe$, R^2 = phthalimido
(8) $R^1 = CO_2Me$, R^2 = phthalimido
(9) $R^1 = CH_2{\cdot}CO_2Me$, R^2 = phthalimido



(10) $R^1 = CO_2{\cdot}CH_2{\cdot}OMe$, R^2 = phthalimido
(11) $R^1 = CO_2Me$, R^2 = phthalimido
(12) $R^1 = CO_2Na$, R^2 = phthalimido
(13) $R^1 = CH_2{\cdot}CO_2Me$, R^2 = phthalimido
(14) $R^1 = CO_2{\cdot}CH_2{\cdot}OMe$, R^2 = *p*-nitrobenzylideneamino
(15) $R^1 = CO_2Me$, R^2 = *p*-nitrobenzylideneamino

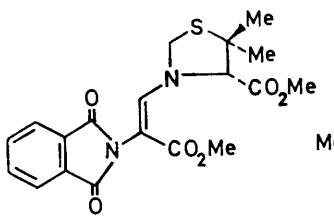
[1] Part VII, J. R. Jackson and R. J. Stoodley, *J.C.S. Perkin I*, 1972, 895.
[2] Preliminary communication, J. R. Jackson and R. J. Stoodley, *Chem. Comm.*, 1970, 14.
[3] S. Wolfe and W. S. Lee, *Chem. Comm.*, 1968, 242; D. A. Johnson, D. Mania, C. A. Panetta, and H. H. Silvestri, *Tetrahedron Letters*, 1968, 1903; J. P. Clayton, J. H. C. Nayler, R. Southgate, and E. R. Stove, *Chem. Comm.*, 1969, 130; D. A. Johnson and D. Mania, *Tetrahedron Letters*, 1969, 267; R. D. G. Cooper, P. V. DeMarco, and D. O. Spry, *J. Amer. Chem. Soc.*, 1969, **91**, 1528; G. E. Gutowski, *Tetrahedron Letters*, 1970, 1779; S. Wolfe, W. S. Lee, and R. Misrae, *Chem. Comm.*, 1970, 1067; B. G. Ramsay and R. J. Stoodley, *ibid.*, 1970, 1517.
[4] B. G. Ramsay and R. J. Stoodley, *Chem. Comm.*, 1971, 450.
[5] J. R. Jackson and R. J. Stoodley, *Chem. Comm.*, 1971, 647.
[6] O. K. J. Kovacs, B. Ekström, and B. Sjöberg, *Tetrahedron Letters*, 1969, 1863.

sodium methoxide was investigated. By analogy with the alkali-induced conversion of an anhydropenicillin into a penicillin,[7] it was expected that the thiazine (16) would afford the racemate of the thiazolidine (22). It was hoped that the structure of the latter could be confirmed by synthesis.



(16) R^1 = Me, R^2 = phthalimido
(17) R^1 = H, R^2 = phthalimido
(18) R^1 = Me, R^2 = *p*-nitrobenzylideneamino
(19) R^1 = H, R^2 = *p*-nitrobenzylideneamino
(20) R^1 = Me, R^2 = NH_2
(21) R^1 = Me, R^2 = (*N*-ethoxycarbonylphthalamoyl)amino

(4*S*)-5,5-Dimethylthiazolidine-4-carboxylic acid [8] reacted with methyl α-phthalimidomalonaldehydate [9] to give a syrupy acid, which afforded a crystalline methyl ester with diazomethane. Spectroscopy left little doubt that the ester, which was obtained in 74% overall yield, was a single geometric isomer possessing either structure (22) or (23).



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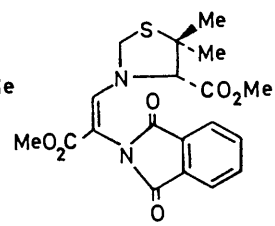


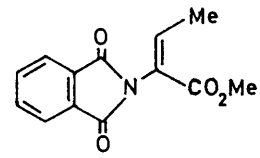
(23)

When briefly treated with methanolic sodium methoxide, the thiazine (16) afforded a syrupy derivative which, by mass spectroscopy, was identical to the above synthetic ester. However, n.m.r. spectroscopy indicated that the two substances were different and that they were probably geometric isomers. The product derived from the thiazine (16) is undoubtedly the racemate of the thiazolidine (22). Moreover, when treated with iodine, the racemate was completely isomerised to a crystalline material which was indistinguishable from the synthetic ester by i.r., n.m.r., and mass spectroscopy. Consequently, the synthetic ester possesses structure (23) and its formation is thermodynamically controlled.

It is worth drawing attention to the fact that the vinylic protons of the thiazolidines (22) and (23) show a notable chemical shift difference: that of the former derivative appears at τ 3·34 while that of the latter at 2·1. Evidently, the proton which is *cis* to the methoxycarbonyl group absorbs at lower field. However, this situation is apparently reversed in the case of α-benzamido-cinnamates [10] and α-phthalimido-crotonates [11] since the proton which is *trans* to the ester group is considered to be more deshielded. Thus, the vinylic protons of compounds (24) and (25) are reported to absorb at τ 2·60 and 3·49, respectively.

The conversion of the penicillanate (1) into the acid (17) involves a dramatic reorganisation. The thiazepine (10) appears to be a reasonable intermediate in this process although it was not detected when the reaction was followed by n.m.r. spectroscopy. Support for its intermediacy was obtained, however, by subjecting the derivative [obtained from the reaction of the salt (12) with chloromethyl methyl ether] to the rearrangement conditions. In the presence of triethylamine the thiazepine (10) was converted into the acid (17) *ca.* 40 times faster than the penicillanate (1). The slow step in the rearrangement, therefore, appears to be the conversion of the penicillanate (1) into the thiazepine (10).

The mode of rearrangement of penicillanic acid derivatives to 1,4-thiazepines has been studied [4] and the rate-determining step is believed to involve a base-catalysed abstraction of the 6-proton. It seemed likely, therefore, that thiazepine formation would be speeded up by increasing the acidity of the 6-proton. Since such a modification is not expected to dramatically influence the rate of formation of the 1,3-thiazine from the 1,4-thiazepine, it should be possible to isolate the latter as an intermediate.



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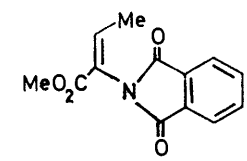
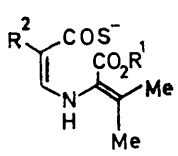


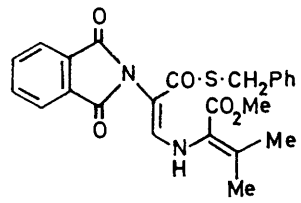
(25)

The above objective was realized in the case of methoxymethyl 6β-*p*-nitrobenzylideneaminopenicillanate (5), obtained from the reaction of methoxymethyl 6β-aminopenicillanate [1] and *p*-nitrobenzaldehyde. On brief treatment with triethylamine, the Schiff base (5) was converted into the thiazepine (14) which was isolated as yellow crystals (38%). Further reaction led to the formation of the thiazine (19) which was characterised as its crystalline methyl ester (18) (34%). The structure of the latter was confirmed by converting it into the thiazine (16). Thus, the imino-group of compound (18) was cleaved by mild acid and the derived amine (20) was condensed *in situ* with ethyl 1,3-dioxoisoindoline-2-carboxylate to yield the phthalamoylamine (21) which afforded the thiazine (16) on treatment with sodium hydrogen carbonate.

[7] S. Wolfe, R. N. Bassett, S. M. Caldwell, and F. I. Wasson, *J. Amer. Chem. Soc.*, 1969, **91**, 7205.
[8] H. T. Clarke, J. R. Johnson, and R. Robinson, 'The Chemistry of Pencillin,' Princeton University Press, Princeton, 1949, p. 958.
[9] J. C. Sheehan and D. A. Johnson, *J. Amer. Chem. Soc.*, 1953, **76**, 158.
[10] A. P. Morgenstern, C. Schuijt, and W. Th. Nauta, *Chem. Comm.*, 1969, 321.
[11] A. G. Brown and T. C. Smale, *Chem. Comm.*, 1969, 1489.

It is clear from the above results that 1,4-thiazepines are the precursors of 1,3-thiazines. The rearrangement requires a cleavage of the 1,2-bond and a migration of the methylene group. In principle, either of these processes may trigger the reorganisation. Thus, intermediate (26), derived from the thiazepine (14) by β-elimination, may be the initially formed species. It is known [6] that the thiazepine (11) reacts with benzyl

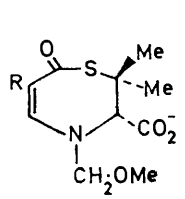




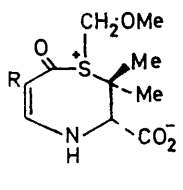
(26) R^1 = CH_2·OMe, R^2 = *p*-nitrobenzylideneamino
(27) R^1 = Me, R^2 = *p*-nitrobenzylideneamino

(28)

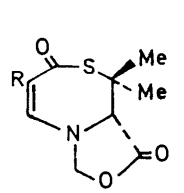
bromide in the presence of sodium methoxide to give compound (28). The conversion of intermediate (26) into the thiazine (19) may involve transfer of the methoxymethylene group to the sulphur or nitrogen atom followed by ring-closure.



(29) R = *p*-nitrobenzylideneamino



(30) R = *p*-nitrobenzylideneamino



(31) R = *p*-nitrobenzylideneamino

Alternatively, the first step of the rearrangement may involve transfer of the methoxymethylene group to give the thiazepines (29) or (30). The former is less likely to undergo β-elimination than the thiazepine (14) (since its 3-proton is more deactivated), and, consequently, it is probably not involved. The zwitterion (30) is a more serious contender than compound (29) since the sulphonium group is expected to increase the acidity of the 3-proton. The lactone (31), which may be formed from compound (29), also merits consideration since its 3-proton is expected to be more acidic than that of the thiazepine (14).

In an attempt to seek some evidence for the mode of conversion of 1,4-thiazepines into 1,3-thiazines, the reactions of the thiazepines (14) and (15) with triethylamine were examined under comparable conditions. If the reorganisation is triggered by the formation of intermediate (26), then the related species (27) should be formed from the thiazepine (15) at a similar rate [the 3-protons of the thiazepines (14) and (15) are expected to be of comparable acidity]. The formation of intermediate (27) may be manifested in either the disappearance or racemisation of the thiazepine (15). Alternatively, if compounds (30) or (31) intervene then the thiazepine (15) is expected to undergo β-elimination much less readily than the thiazepine (14).

Initially, the reactions of the thiazepines (14) and (15) with triethylamine were followed polarimetrically. Under conditions in which the rotation of the former fell to zero that of the latter was virtually unchanged and, therefore, it was inferred [2] that intermediates (30) or (31) were implicated in the rearrangement. However, when these reactions were monitored by n.m.r. spectroscopy it became clear that the thiazepine (15) did react and, indeed, it was converted into a complex mixture of products. The n.m.r. spectrum of the mixture showed the presence of signals in the τ 7·5—9·0 region which implied that at least some of the constituents were derived by β-elimination. Under conditions in which the conversion of the thiazepine (14) into the acid (19) was 50% complete in 3 h, the thiazepine (15) required *ca.* 14 h to react to a comparable extent. The latter experiment was repeated on a larger scale and left for 160 h. Chromatography over alumina led to the recovery (*ca.* 10%) of the thiazepine (15), $[\alpha]_D$ +76° ($CHCl_3$). Consequently, it undergoes little or no racemisation in the presence of triethylamine, implying that the β-elimination to give intermediate (27) is irreversible. Since the difference in reactivity of the thiazepine (14) and (15) appears to be only slight, the formation of intermediate (26) probably represents the first step in the conversion of the thiazepine (14) into the acid (19).

EXPERIMENTAL

For general experimental details see Part I.[12]

Reaction of Methoxymethyl 6β-Phthalimidopenicillanate (1) with Triethylamine.—Triethylamine (34 mg, 0·3 mmol) was added to a solution of the ester [1] (1) (0·117 g, 0·3 mmol) in deuteriochloroform (0·35 ml). After 4 d the solution was diluted with chloroform and shaken with sodium hydrogen carbonate solution. The organic layer was washed with N-hydrochloric acid followed by water, dried ($MgSO_4$), and evaporated to leave a pale yellow syrup (0·029 g, 25%) which, on the basis of n.m.r. spectroscopy, was methoxymethyl 6α-phthalimidopenicillanate (7). The material crystallised from ethanol, m.p. 174—176° (lit.,[1] 174—176°).

The sodium hydrogen carbonate solution was acidified with N-hydrochloric acid and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and concentrated to afford 2-(3,6-dihydro-6-oxo-5-phthalimido-2*H*-1,3-thiazin-3-yl)-3-methylbut-2-enoic acid (17) as a pale yellow amorphous solid (0·068 g, 63%), $\nu_{max.}$ (KBr) 1770 and 1710 (phthalimido C=O), 1710 (acid C=O), and 1595 cm^{-1}, τ ($CDCl_3$) 7·86 and 7·82 (each 3H, s, *gem*-Me_2), 5·03br (2H, s, CH_2), 2·98 (1H, s, vinylic H), 2·19 (4H, s, aromatic protons), and 0·68br (1H, s, CO_2H). With diazomethane the acid afforded the *methyl ester* (16) as pale yellow crystals, m.p. 116—117° [from chloroform–light petroleum (b.p. 60—80°)], $[\alpha]_D$ 0° (1·0% in $CHCl_3$), $\nu_{max.}$ (KBr) 1780 and 1715 (phthalimido C=O), 1715 (ester C=O), and 1605 cm^{-1}, $\lambda_{max.}$ (EtOH) 226 (ε 18,000), 260 (6500), and 326 (8300) nm, τ ($CDCl_3$) 7·76 and 7·71 (each 3H, s, *gem*-Me_2), 6·15 (3H, s, OMe), 5·03 (2H, s, SCH_2), 3·03 (1H, s, vinylic H), and 2·14 (4H, m, aromatic protons) [Found: C, 54·4; H, 4·1; N,

[12] I. McMillan and R. J. Stoodley, *J. Chem. Soc.* (*C*), 1968, 2533.

6·85. $C_{18}H_{16}N_2O_5S,0·25CHCl_3$ requires C, 54·5; H, 4·05; N, 6·95%. *M* (mass spectrum), 372·0793. $C_{18}H_{16}N_2O_5S$ requires 372·0780]. The mass spectrum showed peaks at *m/e* 83, 85, and 87 (in the ratio of 9 : 6 : 1) indicating that the sample contained chloroform.

Methyl (Z)-β-[4(S)-*Methoxycarbonyl*-5,5-*dimethylthiazolidin*-3-*yl*]-α-*phthalimidoacrylate* (23).—Methyl α-phthalimidomalonaldehydate [9] (0·136 g, 0·55 mmol) and 4(*S*)-5,5-dimethylthiazolidine-4-carboxylic acid [8] (0·0886 g, 0·55 mmol) were dissolved in methanol (9 ml). After 4 d the solvent was evaporated to leave a pale yellow syrup which, on the basis of n.m.r. spectroscopy, was β-[(*S*)-carboxy-5,5-dimethylthiazolidin-3-yl]-α-phthalimidoacrylate, τ ($CDCl_3$) 8·56 and 8·42 (each 3H, s, *gem*-Me_2), 6·34 (3H, s, CO_2Me), 5·76 (1H, s, 4-H), 5·30 (2H, ABq, *J* 8 Hz, CH_2), 2·06 (4H, m, aromatic protons), 1·88 (1H, s, vinylic H), and 1·06br (1H, s, CO_2H).

The acid afforded the crystalline *methyl ester* (23) (0·158 g, 71%) with diazomethane, m.p. 128—129° (from ethanol–water), $[\alpha]_D$ +156° (0·97% in $CHCl_3$), $\nu_{max.}$ (KBr) 1785 and 1720 (phthalimido C=O), 1750 (ester C=O), 1690, and 1640 cm^{-1}, $\lambda_{max.}$ (EtOH) 225 (ε 18,700), 239 (12,500), and 275 (25,800) nm, τ ($CDCl_3$) 8·67 and 8·46 (each 3H, s, *gem*-Me_2), 6·40 and 6·32 (each 3H, s, CO_2Me), 5·74 (1H, s, 4-H), 5·29 (2H, ABq, *J* 8 Hz, CH_2), and 2·1 (5H, m, vinylic and aromatic protons) [Found: C, 56·4; H, 4·85; N, 7·05%; *M* (mass spectrum), 404. $C_{19}H_{20}N_2O_6S$ requires C, 56·4; H, 5·0; N, 7·05%; *M*, 404].

Reaction of the Thiazine (16) *with Sodium Methoxide*.—Methanolic 3·8N-sodium methoxide (0·5 ml, 1·9 mmol) was added to a stirred suspension of the thiazine (16) (0·10 g, 0·269 mmol) in methanol (5 ml). After 30 min the solution was diluted with water and shaken with chloroform. The organic layer was washed twice with water, dried ($MgSO_4$), and evaporated to give the (*E*)-thiazolidine (22) as a pale yellow syrup (0·066 g, 61%), $\nu_{max.}$ (film) 1780 and 1720 (phthalimido C=O), 1750 (ester C=O), and 1615 cm^{-1}, τ ($CDCl_3$) 8·52 and 8·38 (each 3H, s, *gem*-Me_2), 6·37 and 6·17 (each 3H, s, CO_2Me), 5·51 (1H, s, 4-H), 5·45 and 4·87 (each 1H, d, *J* 8 Hz, CH_2), 3·34 (1H, s, vinylic H), and 2·16 (4H, m, aromatic protons) [Found: *M* (mass spectrum), 404. Calc. for $C_{19}H_{20}N_2O_6S$: *M*, 404]. The mass spectrum was identical to that of the synthetic thiazolidine (23).

Reaction of the Thiazolidine (22) *with Iodine*.—A small crystal of iodine was added to a solution of the thiazolidine (22) (0·05 g) in deuteriochloroform (0·4 ml) and the reaction was followed by n.m.r. spectroscopy. After 2 h, when the n.m.r. spectrum of the sample was identical to that of compound (23), the solution was diluted with chloroform, washed with sodium thiosulphate solution followed by water, and dried ($MgSO_4$). Evaporation of the solvent left a syrup which crystallised from aqueous ethanol to afford the racemate of the thiazolidine (23) (0·017 g, 34%), m.p. 112—114°. The i.r. and mass spectrum of the material were identical to those of the thiazolidine (23).

Methoxymethyl (3S)-2,3,4,7-*Tetrahydro*-2,2-*dimethyl*-7-*oxo*-6-*phthalimido*-1,4-*thiazepine*-3-*carboxylate* (10).—The sodium salt (12) was prepared by the procedure of Ramsay.[13] Sodium iodide (3·0 g, 0·02 mol) was added to a solution of methyl 6β-phthalimidopenicillanate (2) (7·2 g, 0·02 mol) in ethyl methyl ketone (100 ml) and the mixture was heated under reflux. After 3 d the crude sodium salt (12) (0·92 g, 12%) was collected by filtration, $[\alpha]_D$ −156° (0·28% in H_2O), $\nu_{max.}$ (KBr) 3320 (NH), 1780 and 1720 (phthalimide C=O), 1620 (unsat. thiolactone), and 1600 (CO_2^-) cm^{-1}, τ (D_2O) 8·32 (6H, s, *gem*-Me_2), 5·65 (1H, s, 3-H), 2·62 (1H, s, vinylic H), and 2·16 (4H, s, aromatic protons).

Chloromethyl methyl ether (0·5 ml, 6·6 mmol) was added to a solution of the salt (12) (0·552 g, 1·5 mmol) in *NN*-dimethylformamide (25 ml) and the solution was stirred at room temperature. After 18 h the solvent was removed by evaporation using first butan-1-ol and then ethyl acetate as azeotropes. The product was purified by alumina chromatography to afford the *methoxymethyl ester* (10) as a pale yellow syrup (0·211 g, 36%), $\nu_{max.}$ (film) 1780 and 1725 (phthalimido C=O), and 1725 (ester C=O) cm^{-1}, τ [$(CD_3)_2SO$] 8·38 and 8·30 (each 3H, s, *gem*-Me_2), 6·53 (3H, s, OMe), 5·54 (1H, d, *J* 7 Hz, collapsed to s on addition of D_2O, 3-H), 4·64 (2H, s, OCH_2), 2·67 (1H, d, *J* 9 Hz, collapsed to s after addition of D_2O, 5-H), 2·06 (4H, s, aromatic protons), and 1·2br (1H, disappeared on addition of D_2O, NH) [Found: *M* (mass spectrum), 390. $C_{18}H_{18}N_2O_6S$ requires *M*, 390].

Reaction of the Thiazepine (10) *with Triethylamine*.—Triethylamine (0·034 g, 0·3 mmol) was added to a solution of the thiazepine (10) (0·111 g, 0·28 mmol) in deuteriochloroform (0·45 ml). The reaction was followed by n.m.r. spectroscopy. After 2·5 h the solution was diluted with chloroform and extracted with sodium hydrogen carbonate solution. The aqueous layer was acidified with N-hydrochloric acid and extracted with chloroform. The chloroform extract was shaken with water, dried ($MgSO_4$) and evaporated to a syrup which was treated with diazomethane. The product possessed an n.m.r. spectrum which was identical to that of the thiazine (16); it crystallised (0·019 g, 17%) from chloroform–light petroleum (b.p. 60—80°), m.p. 116—117°.

Methoxymethyl 6β-p-*Nitrobenzylideneaminopenicillanate* (5).—A suspension of the toluene-*p*-sulphonic acid salt of methoxymethyl 6β-aminopenicillanate [1] (10·4 g, 0·025 mol) in dichloromethane (100 ml) was shaken with a solution of sodium hydrogen carbonate (2·3 g, 0·027 mol) in water (75 ml). The organic layer was washed with water (3 times), dried ($MgSO_4$), and evaporated to afford methoxymethyl 6β-aminopenicillanate as a pale yellow syrup.

p-Nitrobenzaldehyde (3·75 g, 0·025 mol) was added to a solution of the amine in dichloromethane (100 ml). After 2 h the solution was dried ($MgSO_4$) and concentrated. Addition of ether to the residue gave the *Schiff base* (5) (6·8 g, 69%) as pale yellow crystals, m.p. 95—96° (from methanol), $[\alpha]_D$ +182° (0·2% in $CHCl_3$), $\nu_{max.}$ (KBr) 1775 (β-lactam C=O), 1755 (ester C=O), 1630 (C=N), 1605, and 1540 and 1350 (aromatic NO_2) cm^{-1}, $\lambda_{max.}$ (EtOH) 285 (ε 16,700), τ ($CDCl_3$) 8·42 and 8·31 (each 3H, s, *gem*-Me_2), 6·46 (3H, s, OMe), 5·54 (1H, s, 3-H), 4·63 (2H, ABq, *J* 6 Hz, OCH_2), 4·50 (1H, dd, *J* 5 Hz and *J* 2 Hz, 6-H), 4·26 (1H, d, *J* 5 Hz, 5-H), 1·87 (4H, ABq, *J* 9 Hz, aromatic protons), and 1·24 (1H, d, *J* 2 Hz, CH=N) [Found: C, 52·3; H, 5·0; N, 11·05%; *M* (mass spectrum), 393·0991. $C_{17}H_{19}N_3O_6S$ requires C, 52·0; H, 4·87; N, 10·7%; *M* 393·0994].

Reaction of the Schiff Base (5) *with Triethylamine*.—(*a*) Triethylamine (0·101 g, 1·0 mmol) was added to a solution of the Schiff base (5) (0·393 g, 1·0 mmol) in chloroform (7 ml). After 23 h the solvent was removed by evaporation and the residue was treated with ethereal diazomethane. The product was purified by alumina chromatography to

[13] B. G. Ramsay, Ph.D. Thesis, University of Newcastle upon Tyne, 1970.

give *methyl* 2-[3,6-*dihydro*-5-(p-*nitrobenzylideneamino*)-6-*oxo*-2H-1,3-*thiazin*-3-*yl*]-3-*methylbut*-2-*enoate* (18) as orange crystals (0·127 g, 34%), m.p. 195—196° (from chloroform–ether), $[\alpha]_D$ 0° (1% in $CHCl_3$), $\nu_{max.}$ (KBr) 1715 (ester C=O), 1625, 1615, 1595, 1560, and 1515 and 1340 (aromatic NO_2) cm^{-1}, $\lambda_{max.}$ (EtOH) 260 (ε 12,400) and 384 (21,800) nm, τ ($CDCl_3$) 7·84 and 7·69 (each 3H, s, *gem*-Me_2), 6·16 (3H, s, OMe), 5·20 (2H, s, CH_2) 2·65 (1H, s, 4-H), 1·93 (4H, ABq, *J* 9 Hz, aromatic protons), and 0·60 (1H, s, CH=N).

(*b*) Triethylamine (0·455 g, 0·45 mmol) was added to a solution of compound (5) (0·354 g, 0·9 mmol) in chloroform (3 ml). After 30 min the solution was diluted with chloroform, washed with 0·1N-acetic acid and water, and dried ($MgSO_4$). Evaporation left an orange syrup which on addition of ethanol deposited yellow crystals (0·136 g, 38%) of *methoxymethyl* (3S)-2,3,4,7-*tetrahydro*-2,2-*dimethyl*-6-p-*nitrobenzylideneamino*-7-*oxo*-1,4-*thiazepine*-3-*carboxylate* (14), m.p. 119—120° (from ethanol), $[\alpha]_D$ −22° (1·98% in $CHCl_3$),* $\nu_{max.}$ (KBr) 1735 (ester C=O), 1630 (C=N), 1610, 1570, 1555, and 1530 and 1340 (aromatic NO_2) cm^{-1}, $\lambda_{max.}$ (EtOH) 258 (ε 10,800) and 388 (15,200) nm, τ ($CDCl_3$) 8·37 (6H, s, *gem*-Me_2), 6·48 (3H, s, OMe), 5·51 (1H, d, *J* 6 Hz, collapsed to s on addition of D_2O, 3-H), 4·62 (2H, s, OCH_2), 3·0br (1H, disappeared on addition of D_2O, NH), 2·31 (1H, d, *J* 9 Hz, collapsed to s on addition of D_2O, 5-H), 1·97 (4H, ABq, *J* 9 Hz, aromatic protons), and 0·66 (1H, s, CH=N) [Found: C, 51·9; H, 4·8; N, 10·9%; *M* (mass spectrum), 393. $C_{17}H_{19}N_3O_6S$ requires C, 51·9; H, 4·85; N, 10·7%; *M*, 393].

Conversion of the Thiazine (18) *into the Thiazine* (16).—2N-Hydrochloric acid (35 ml) was added to a solution of compound (18) (0·77 g, 0·2 mmol) in acetone (35 ml). After 10 min the solution was diluted with water and washed with chloroform. The aqueous layer was neutralised with sodium hydrogen carbonate solution and extracted with chloroform which was washed with water and dried ($MgSO_4$). The solvent was partially evaporated to yield a solution of the amine (20) in chloroform (*ca.* 20 ml) [total removal of the solvent left the amine (20) as a very unstable syrup]. The solution was treated with ethyl 1,3-dioxoisoindoline-2-carboxylate (0·438 g, 2·0 mmol) and, after 22 h, the solvent was removed by evaporation to afford *methyl* 2-[5-(N-*ethoxycarbonylphthalamoyl*)*amino*-3,6-*dihydro*-6-*oxo*-2H-1,3-*thiazin*-3-*yl*]-3-*methylbut*-2-*enoate* (21) as pale yellow crystals (0·744 g, 81%), m.p. 121—122 [from chloroform–light petroleum (b.p. 60—80°)], $\nu_{max.}$ 1770 and 1725 (urethane C=O), 1725 (ester C=O), 1645, 1635, and 1605 cm^{-1}, τ ($CDCl_3$) 8·78 (3H, t, *J* 8 Hz, CH_3CH_2), 7·91 and 7·76 (each 3H, s, *gem*-Me_2), 5·84 (2H, q, *J* 8 Hz, CH_3CH_2), 5·22 (2H, s, $S{\cdot}CH_2N$), 2·48 (4H, s, aromatic protons), 2·02 (1H, s, 4-H), and 1·88 and 1·21 (each 1H, s, disappeared on addition of D_2O, NH).

Sodium hydrogen carbonate (0·0924 g, 1·1 mmol) in water (25 ml) was added to the phthalamoyl-ester (21) (0·426 g, 1·1 mmol) in acetone (25 ml). After 5 min the solution was diluted with water and extracted with chloroform. The extract was dried ($MgSO_4$) and the solvent was removed by evaporation. The residue was dissolved in light petroleum (b.p. 60—80°) and the solution deposited pale yellow crystals of the thiazine (16) (0·303 g, 91%), m.p. 116—117°.

Methyl 3S-2,3,4,7-*Tetrahydro*-2,2-*dimethyl*-6-p-*nitrobenzylideneamino*-7-*oxo*-1,4-*thiazepine*-3-*carboxylate* (15).—Triethylamine (4·048 g, 0·04 mol) and *p*-nitrobenzaldehyde (3·02 g, 0·02 mol) were added to a suspension of 6β-aminopenicillanic acid (4·32 g, 0·02 mol) in dichloromethane (75 ml). After stirring at room temperature for 2 h, the solution was treated with diazomethane in ether. Evaporation of the solvent left a red syrup which deposited crystals of the *thiazepine* (15) (3·14 g, 42%) on addition of ethyl acetate, m.p. 172—173° (decomp.) (from ethyl acetate), $[\alpha]_D$ +80° (0·2% in $CHCl_3$), $\nu_{max.}$ (KBr) 1730 (ester C=O), 1625 (C=N), 1605, 1570, and 1535 and 1340 (aromatic NO_2) cm^{-1}, $\lambda_{max.}$ (EtOH) 259 (ε 11,600) and 388 (17,300) nm, τ ($CDCl_3$) 8·60 and 8·40 (each 3H, s, *gem*-Me_2), 6·12 (3H, s, OMe), 5·49 (1H, d, *J* 6 Hz, collapsed to s on addition of D_2O, 3-H), 3·5br (1H, disappeared on addition of D_2O, NH), 2·06 (1H, d, *J* 9 Hz, collapsed to s on addition of D_2O, 5-H), 1·96 (4H, ABq, *J* 9 Hz, aromatic protons), and 0·63 (1H, s, CH=N) [Found: C, 53·0; H, 4·7; N, 11·5%; *M* (mass spectrum), 363. $C_{16}H_{17}N_3O_5S$ requires C, 52·9; H, 4·7; N, 11·6%; *M* 363].

Reactions of the Thiazepines (14) *and* (15) *with Triethylamine.*—(*a*) Triethylamine (0·04 ml), was added to a solution of the thiazepine [(14) or (15)] (0·05 mmol) in deuteriochloroform (0·8 ml) in an n.m.r. tube at 33° and the reactions were followed by n.m.r. spectroscopy.

The reaction of the former was followed by observing the disappearance of the signal at τ 8·39 [due to the *gem*-Me_2 group of the thiazepine (14)] and the appearance of the signals at τ 8·00 and 7·73 [due to the *gem*-Me_2 group of the thiazine (19)]. The rearrangement reached half completion in *ca.* 3 h.

The reaction of the latter was followed by the disappearance of the signal at τ 0·55 [due to the CH=N proton of the thiazepine (15)]. It was half complete in *ca.* 14 h. When no more starting material could be detected, the solution was diluted with chloroform, washed with dilute hydrochloric acid followed by water, dried ($MgSO_4$), and evaporated to an orange syrup (0·017 g). The n.m.r. spectrum ($CDCl_3$) of the product showed that a complex mixture was present; the signals at τ 7·5—8·0 (characteristic of Me groups attached to a double bond) accounted for *ca.* 25% of the signals in the 7·5—9·0 region.

(*b*) Triethylamine (0·48 ml, 3·5 mmol) was added to a solution of the thiazepine (15) (0·254 g, 0·7 mmol) in chloroform (10 ml). After 160 h the solution was evaporated to a dark syrup which was fractionated on an alumina column using chloroform as eluant. Some starting material (0·025 g, 10%) was isolated from the third set of fractions; it crystallised from ethanol, m.p. 168—171° (decomp.), $[\alpha]_D$ +76° (0·24% in $CHCl_3$).

We thank Dr. J. H. C. Nayler for his interest and Mr. P. Kelly for the mass spectral determinations. One of us (J. R. J.) thanks Beecham Research Laboratories for a maintenance grant.

[1/2219 *Received*, 23*rd November*, 1971]

* The value of +7° reported in the preliminary communication [2] is in error.