Studies related to Penicillins. Part 20.[1] The Mechanism of the Rearrangement of Methyl Benzylpenicillinate to Methyl Benzylpenillonate

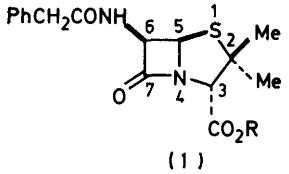
By **Rajiv Sharma** and **Richard J. Stoodley,*** Department of Organic Chemistry, The University, Newcastle upon Tyne, NE1 7RU

In boiling benzene containing a trace of iodine, methyl benzylpenicillinate (1) isomerises to methyl benzylpenillonate (10a). The rearrangement is triggered by a 4,7-bond cleavage of the penicillinate (1a) and probably involves the formation of methyl (4*S*)-2-[(5*R*)-2-benzyl-4-oxo-Δ^2-oxazolin-5-yl]-5,5-dimethylthiazolidine-4-carboxylate (9a) as the primary intermediate. This intermediate undergoes an irreversible fragmentation to methyl (4*S*)-5,5-dimethyl-Δ^2-thiazoline-4-carboxylate (8a) and 2-benzyl-Δ^2-oxazolin-4-one (5), which then combine to give the penillonate (10a), probably by way of the species (24).

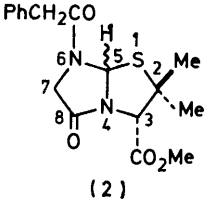
The reaction pathway is, however, complicated by the preferential reaction of the primary intermediate (9a) with the thiazoline (8a) to give dimethyl (3*R*,4*R*,7*S*,12*S*)-2-oxo-3-phenylacetamido-6,6,11,11-tetramethyl-5,10-dithia-1,8-diazatricyclo[7.3.0^{4,8}]dodecane-7,12-dicarboxylate (20a). On the basis of deuterium-labelling experiments, it is shown that the aforementioned addition reaction is reversed in the presence of hydrogen iodide. Therefore the tricyclododecane (20a) is not a direct intermediate in the penicillinate→penillonate transformation but it is formed in a reversible side-reaction.

THE conversion of methyl benzylpenicillinate (1a) into methyl benzylpenillonate (2) was one of the early encountered penicillin rearrangements.[2] The reorganisation was conveniently effected in boiling toluene containing a trace of iodine (3 h); under these conditions the yield of once-recrystallised product was *ca.* 33%.

Three proposals have been forwarded to account for



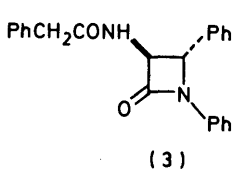
(1)



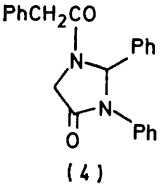
(2)

a; R = Me c; R = CD_3
b; R = CO_2Et d; R = K

the isomerisation. Woodward † suggested a mechanism involving cleavage of the 5,6-bond of the penicillinate (1a) and attack of the phenylacetamido-nitrogen atom at position 5.[3] Bird[4] noted that the azetidinone (3), when heated with iodine in xylene, gave the imidazolidinone (4). Since the oxazolidinone (5) and *N*-benzylideneaniline were not intermediates in the foregoing reaction, it was suggested that the species (6) and (7)

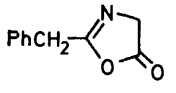


(3)

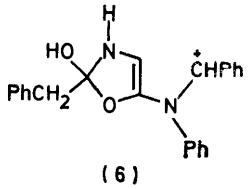


(4)

intervened. By analogy, it was proposed that the penicillinate→penillonate transformation proceeded by way of related intermediates. Jansen and Robinson[5] demonstrated that the penillonate (2) was formed (38%) by heating the oxazolinone (5) and the thiazoline (8a) in benzene (20 h). They considered that the penicillinate→penillonate transformation was triggered by the 4,7-bond cleavage, involving the thiazolidine–oxazoline



(5)

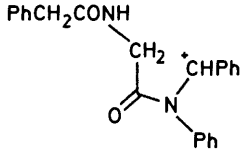


(6)

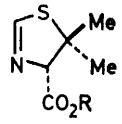
(9a) as the primary intermediate. Species (9a) was then postulated to undergo fragmentation to the derivatives (5) and (8a), which reacted to give the penillonate (2).

RESULTS AND DISCUSSION

In an attempt to unravel the reaction pathway, the penicillinate→penillonate rearrangement has been re-

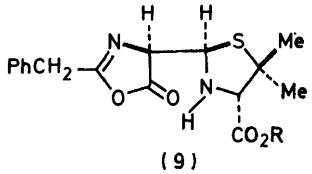


(7)



(8)

a; R = Me
b; R = CD_3



(9)

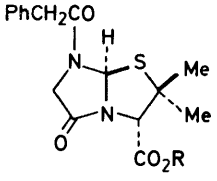
a; R = Me
b; R = CD_3

examined; we now report the results of this study. It was found that the isomerisation proceeded under milder conditions than previously reported. When heated in

† See, however, ref. 2, p. 160 (footnote).

benzene containing 0.01% iodine (20 h), the penicillinate (1a) afforded the penillonate (2) in 70% yield (after silica gel chromatography). A recrystallised sample of the penillonate (2) melted at 148—150 °C and possessed an optical rotation of +314° (MeOH), in good agreement with the literature values.[2] N.m.r. spectroscopy, in addition to supporting the structure (2), indicated that the derivative existed in solution ($CDCl_3$) as a 2 : 1 mixture of isomers. Thus the spectrum showed two singlets at δ 4.84 and 4.91, assigned to the 3-proton of the thiazolidine ring, and two singlets at 7.08 and 7.21, attributed to the bridgehead proton. Variable-temperature studies left little doubt that the isomers were rotamers, arising because of restricted rotation of the phenylacetamido-moiety. At 70 °C, the signals at 4.84 and 4.91 coalesced to a sharp singlet at 4.87 whereas those at 7.08 and 7.21 appeared as a broad singlet at 7.13; the original spectrum was restored when the solution was returned to the initial temperature (26 °C). Although the stereochemistry at the bridgehead position is not defined by the foregoing method, it is clear that methyl benzylpenillonate (2) is a single compound. A recent *X*-ray crystallographic study [6] has established that the bridgehead hydrogen atom is α-orientated and that the penillonate possesses the stereostructure (10a).

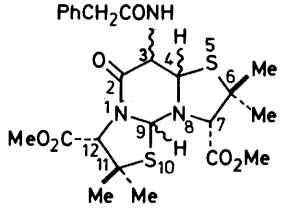
Derivatives (1a) and (10a) were readily distinguished on t.l.c., the latter material being more mobile than the former. When the thermolysis of the penicillinate (1a)



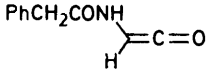
(10)

a ; R = Me

b ; R = CD_3



(11)



(12)

(13)

was monitored on t.l.c., it was found that the starting material was replaced within a few minutes by two new components. Component (A), which appeared as a white spot when the plate was developed in iodine vapour, was more mobile than the penillonate (10a). Component (B) possessed a chromatographic mobility which was between that of the penicillinate (1a) and the penillonate (10a). As the thermolysis proceeded, components (A) and (B) disappeared and were replaced by the penillonate (10a). When the penicillinate (1a) (0.500 g) was thermolysed for 30 min and the product fractionated by silica gel chromatography, the penillonate (10a) (0.134 g) and component (B) (0.240 g) were isolated; component (A) was not recovered from the column. Elemental analysis and mass spectroscopy established that component (B), m.p. 133—135 °C, $[\alpha]_D$ +218° ($CHCl_3$), possessed the formula, $C_{24}H_{31}N_3O_6S_2$. N.m.r. spectroscopy left little doubt that it was a single diastereoisomer [designated isomer (A)] of the tricyclododecane (11). In particular, the spectrum ($CDCl_3$) contained singlets at δ 4.11 and 4.70, assigned to the protons adjacent to the methoxycarbonyl groups (the lower-field signal was attributed to the hydrogen atom at position 12 since it was expected to be deshielded compared with that at position 7, due to the acyl substituent on the adjacent nitrogen atom), a triplet at 5.03 ($J = J' = 6$ Hz), due to the proton at position 3, and a doublet at 5.85 (J 6 Hz), attributed to the proton at position 4; the bridgehead proton at position 9 appeared as a singlet at 6.38.

The conversion of the penicillinate (1a) into the tricyclododecane (11) must be accompanied by the formation of a *N*-phenylacetylglycyl moiety. When the penicillinate (1a) was thermolysed for 4 min and the thermolysate treated with benzylamine, the benzylamide of *N*-phenylacetylglycine was isolated in 9% yield. This result is consistent with the intervention of one of the three species (5), (12), and (13). That the oxazolinone (5) was the actual intermediate was deduced by the observation that its chromatographic behaviour was identical with that of component (A). Moreover, the oxazolinone (5) showed a characteristic carbonyl absorption at 1 825 cm^{-1} in its i.r. spectrum; the product derived from the thermolysis of the penicillinate (1a) after 4 min showed a similar absorption.

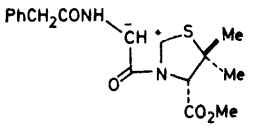
The foregoing results pose two questions. How are the derivatives (5) and (11) formed from the penicillinate (1a) and how are they converted into the penillonate (10a)?

There are several possible answers to the former question. Thus the penicillinate (1a) may undergo a fragmentation to the oxazoline (5) and the thiazoline (8a); these species may then combine to give the derivative (11). However, when a 1 : 1 mixture of the derivatives (5) and (8a) was heated in benzene containing iodine for 3 min, the penillonate (10a) was isolated in 75% yield (after silica gel chromatography). It seems likely therefore that the derivative (11) is produced from the reaction of the thiazoline (8a) with the penicillinate (1a) or, more probably, a species derived from the penicillinate (1a). In support of this possibility, the tricyclododecane was obtained in 66% yield (after silica gel chromatography) when a 1 : 1 mixture of the penicillinate (1a) and the thiazoline (8a) was subjected to the thermolysis conditions.

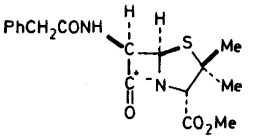
The species (14) and (15) (or equivalent intermediates), formed by respective 5,6- and 4,7-bond ruptures of the penicillinate (1a), warrant consideration as precursors of the tricycle (11). In principle, a distinction between these intermediates may be made by examining the thermolyses of penicillinates which are epimeric at positions 6 and/or 5. If the 5,6-bond rupture takes place, then the penicillinates (1a), (16), and (17) are expected to yield the species (14) as a common inter-

mediate; the species (14) should then react with thiazoline (8a) to give the same diastereoisomer of the tricycle (11). However, if 4,7-bond fission is involved, different diasteroisomers of structure (11) will be produced; their stereochemistries at positions 3 and 4 will reflect those of their penicillinate precursors at positions 5 and 6.

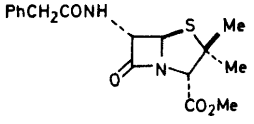
When heated in benzene containing iodine, methyl



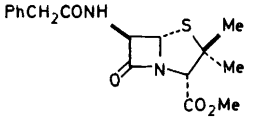
(14)



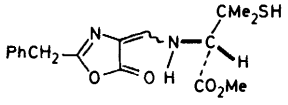
(15)



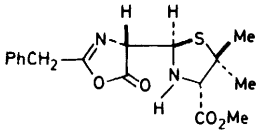
(16)



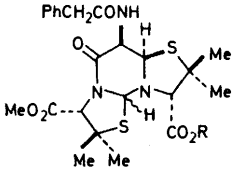
(17)



(18)

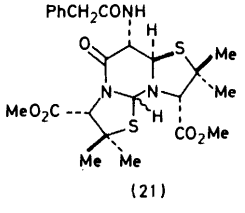


(19)

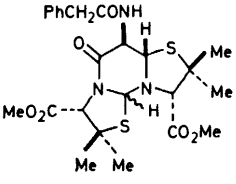


(20)

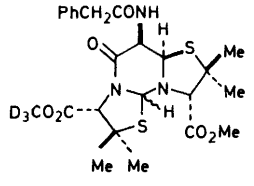
a; R = Me b; R = CD_3



(21)



(22)



(23)

benzyl-6-epipenicillinate (16) was converted within 0.5 h into methyl benzylpenicillenate (18), isolated in 50% yield (after silica gel chromatography). Evidently, compound (16) does not react in a manner analogous to the penicillinate (1a). Nevertheless, it seems likely that the oxazoline–thiazolidine (19), formed from the 6-epipenicillinate (16) by a 4,7-bond cleavage, is the precursor of the penicillenate (18). In the hope of trapping the species (19) the thermolysis of the 6-epipenicillinate (16) was conducted in the presence of the thiazoline (8a). No new product was detected when 1 mol equiv. of the thiazoline (8a) was employed; however, with 4 mol equiv. of the thiazoline (8a), an adduct (23% after silica gel chromatography) was isolated. Spectroscopic considerations indicated that the adduct, m.p. 141—142 °C, $[\alpha]_D$ +149° ($CHCl_3$), was a second diastereoisomer [designated isomer (B)] of the tricyclododecane (11). Its n.m.r. spectrum ($CDCl_3$) showed singlets at δ 3.94 and 4.95, attributed to the protons adjacent to the methoxycarbonyl groups, a double doublet at 4.34 ($J = J' = 9$ Hz), assigned to the proton at position 3, and a doublet at 5.16 (J 9 Hz), due to the proton at position 4; the bridgehead proton at position 9 resonated as a singlet at 6.12.

Methyl benzyl-5-epipenicillinate (17) was converted into two products, which were separated by silica gel chromatography, when heated in benzene containing iodine for 0.25 h. The more-mobile compound (28%) was the penillonate (10a). The less-mobile material (54%), $[\alpha]_D$ +128° ($CHCl_3$), was considered to be a third diastereoisomer [designated isomer (C)] of the tricyclododecane (11), on the basis of its spectroscopic properties. In particular, its n.m.r. spectrum ($CDCl_3$) possessed singlets at 3.57 and 5.01, for the protons adjacent to the methoxycarbonyl groups, a double doublet at 4.47 (J 8 and J' 10 Hz), attributed to the proton at position 3, and a doublet at 5.09 (J 8 Hz), for the proton at position 4; the bridgehead proton at position 9 appeared as a singlet at 6.95. When a 1 : 1 mixture of the 5-epipenicillinate (17) and the thiazoline (8a) was subjected to the thermolysis conditions, isomer (C) of the tricyclododecane (11) was isolated in 64% yield (after silica gel chromatography).

On the basis of the foregoing results, it is clear that the stereochemistries at positions 3 and 4 of the tricyclododecanes of type (11) are identical with those at positions 5 and 6 of their penicillinate precursors. Accordingly, isomer (A) possesses the stereostructure (20a), isomer (B) the stereostructure (21), and isomer (C) the stereostructure (22); the available evidence does not enable the stereochemistry at position 9 to be defined. It is noteworthy that the proton at position 7 of the derivative (22) (δ 3.57) was significantly shielded compared with those of the derivatives (20a) and (21) (δ 4.11 and 3.94, respectively). This effect, originally noted in monocyclic thiazolidines[7] and, more recently, in penicillinates,[8,9] is consistent with the *cis*-arrangement of the protons at positions 4 and 7 in the compound (22).

The mode of formation of the tricyclododecane (20a) and the oxazolinone (5) from the penicillinate (1a) can now be defined. The first step in the reaction probably involves the formation of the oxazolinone–thiazolidine (9a), which undergoes a partial fragmentation to the thiazoline (8a) and the oxazolinone (5). The thiazoline (8a) then reacts with the species (9a) to give the tricyclododecane (20). Evidently, the last-described process takes place more rapidly than the reaction of the

oxazolinone (5) with the thiazoline (8a) to give the penillonate (10a).

The route for the conversion of the tricyclododecane (20a) and the oxazolinone (5) into the penillonate (10a) will now be discussed. In principle, the oxazolinone (5) may combine with both or with one of the masked thiazoline moieties incorporated in the tricyclododecane (20a). Consequently, the thermolysis of an appropriately labelled tricyclododecane. *e.g.* (20b), *in the absence of the oxazoline* (5), may lead to the penillonate (10a) and/or the penillonate (10b).

It was expected that the tricyclododecane (20a) would afford a 1 : 1 mixture of the penillonate (10a) and the thiazoline (8a) when heated in benzene containing iodine. However, when subjected to these conditions for 3.5 h [conditions under which the penicillinate (1a) afforded a 55% yield of the penillonate (10a)], derivative (20a) was recovered largely unchanged (72%) and only a low conversion (10%) into the penillonate (10a) was observed. This result suggested that either the products (8a) and (10a) were in equilibrium with and were less stable than the reactant (20a) or an additional species was necessary to promote the reaction. The former possibility was excluded by the observation that a 1 : 1 mixture of the penillonate (10a) and the thiazoline (8a) was recovered unchanged, when thermolysed in boiling benzene containing iodine for 3.5 h. Furthermore, when a 1 : 1 mixture of the tricyclododecane (20a) and the oxazolinone (5) was similarly thermolysed, little reaction occurred.

It is clear that when the penicillinate (1a) is heated in benzene containing iodine, a species is produced in addition to the oxazolinone (5a) and the tricyclododecane (20a); this species acts as a catalyst for the conversion of the derivatives (5) and (20a) into the penillonate (10a). To shed further light on the nature of the catalyst, the penicillinate (1a) was thermolysed for 0.5 h and the reaction was quenched by cooling. The thermolysate, which contained a mixture of the derivative (5), (10a), and (20a) (t.l.c.), was divided into two portions. One portion was reheated and the progress of the reaction was monitored by t.l.c. The formation of the penillonate (10a) appeared to be complete within 18 h; from this experiment, the penillonate (10a) was isolated in 70% yield (after silica gel chromatography). The second portion was evaporated to dryness and the residue was redissolved in an equivalent volume of benzene containing iodine. The solution was then heated and a time of 43 h was required to effect the formation of the penillonate (10a); the derivative (10a) was isolated in 68% yield (after silica gel chromatography) from this experiment.

The foregoing observations imply that the catalytic species is volatile and therefore probably hydrogen iodide. In support of this supposition, it was found that the tricyclododecane (20a) was converted into the penillonate (10a) (60% after silica gel chromatography) when heated for 3.5 h in benzene saturated with hydrogen iodide

To explore the mode of decomposition of the tricyclododecane (20a), attention was turned to the preparation of the trideuteriated derivatives (20b) and (23). Treatment of the mixed anhydride (1b) with [$^2H_3$]methanol gave the trideuteriated penicillinate (1c). When heated in benzene containing iodine, a 1 : 1 mixture of compounds (1c) and (8a) afforded the trideuteriated tricyclododecane (20b). Under similar conditions, a 1 : 1 mixture of the undeuteriated penicillinate (1a) and the trideuteriated thiazoline (8b) gave the trideuteriated tricyclododecane (23). On the basis of n.m.r. spectroscopy compounds (20b) and (23) were >95% trideuteriated. The trideuteriated tricyclododecanes (20b) and (23) were thermolysed in benzene containing hydrogen iodide for 3.5 h and, in each case, the crude product was purified by silica gel chromatography. In the former instance, the penillonate was found to be 50% trideuteriated; in the latter case, the penillonate was shown to be 52% trideuteriated.

The foregoing results clearly establish that the masked thiazoline moieties of the tricyclododecane (20a) become equivalent during the formation of the penillonate (10a). In a control reaction, it was shown that the trideuteriated penillonate (10b) (>95% $^2H_3$ by n.m.r. spectroscopy) lost *ca.* 25% of its deuterium when it was heated in benzene containing hydrogen iodide with 1 mol equiv. of the undeuteriated thiazoline (8a). Evidently, the formation of the penillonate (10a) is only partially reversible under the conditions required to convert the tricyclododecane (20a) into the penillonate (10a). Accordingly, it seems probable that the tricyclododecane (20a) reverts to a 1 : 2 mixture of the oxazolinone (5) and the thiazoline (8a); compounds (5) and (8a) then combine to give the penillonate (10a). The tricyclododecane (20a) is not a direct intermediate in the transformation of the penicillinate (1a) into the penillonate (10a) but it is formed reversibly in a side reaction. A reaction sequence, which accounts for the present results, is suggested in the Scheme.

In conclusion, the present investigation invalidates the suggestions of Woodward [3] † and Bird [4] regarding the mechanism of the penicillinate→penillonate rearrangements. The results, however, strongly support the proposals of Jansen and Robinson.[5]

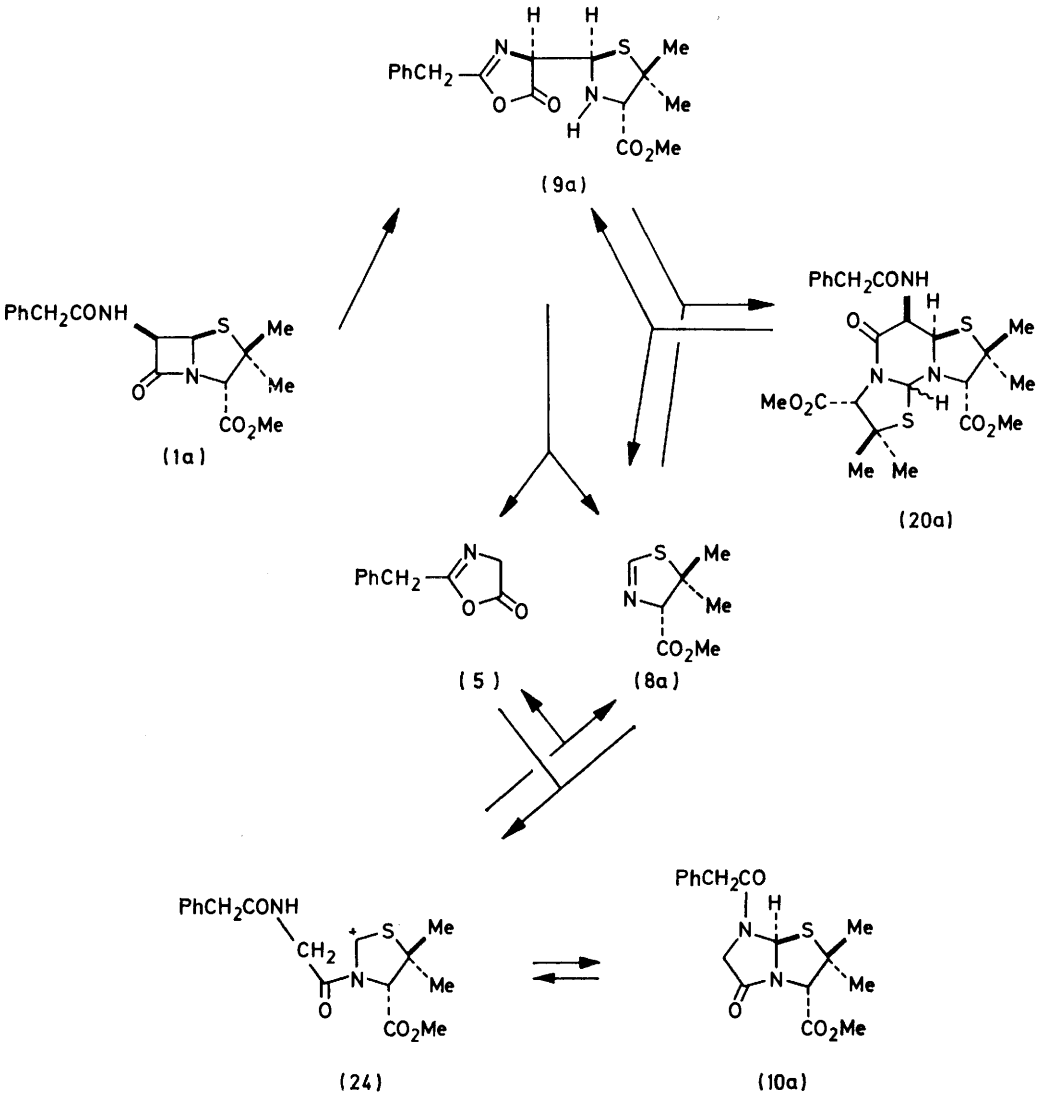
EXPERIMENTAL

Benzene, employed in the thermolyses, was dried over sodium wire. Dichloromethane, used in the preparation of the penicillinate (1c), was distilled from sodium hydroxide and dried over calcium chloride.

Column chromatography was effected under pressure, using Merck Kieselgel H (Typ 60); unless otherwise stated, benzene–ether (9 : 1) was used as the eluting solvent. T.l.c. was performed on Schleicher and Schüll plastic sheets coated with silica gel (F1500 LS 254); the plates were developed with iodine vapour.

Evaporations were carried out at *ca.* 40 °C using a Buchi rotary evaporator. Melting points were determined using a Kofler hot-stage apparatus. A Bendix-Ericson automatic polarimeter was used to measure optical rotations.

I.r. spectra were recorded using a Hilger and Watts Infrascan. A Unicam SP 800 spectrometer was employed to determine u.v. spectra. N.m.r. spectra refer to tetramethylsilane as the internal standard; the spectra were measured at 60 MHz using a Varian EM 360 spectrometer or at 90 MHz using a Brucker Spectrospin HFX-90. Mass spectra were determined using an A.E.I. MS9 spectrometer



SCHEME

operating at 70 eV. Microanalyses were performed with a Hewlett-Packard 185 CHN Analyser.

The deuterium contents of the penillonates (10b) were determined by 90 MHz spectroscopy. Several spectra (5—8) were recorded and stored in the memory of a Fabriteck 1074 Signal Averaging System. The spectra were then integrated and, after base-line correction, the heights of the steps corresponding to the methoxycarbonyl and benzylic methylene protons were determined digitally on an oscilloscope.

Thermolysis of the Penicillinate (1a).—(*a*) The penicillinate (1a) [10] (0.500 g) was heated in benzene (50 cm^3) containing 0.01% iodine for 20 h. Evaporation and purification of the product by silica gel chromatography afforded methyl benzylpenillonate (10a) (0.350 g, 70%); m.p. 148—150 °C (from MeOH) (lit.,[2] 152—154 °C); $[\alpha]_D$ +314° (1.0% in MeOH) {lit.,[2] $[\alpha]_D$ +318° (MeOH)}; $\nu_{max.}$ (KBr) 1 755 (ester CO), 1 730 (imidazolidinone CO), and 1 660 cm^{-1} (amide CO); $\lambda_{max.}$ (EtOH) 215 nm (ε 10 800); δ($CDCl_3$, 90 MHz) 1.53 and 1.58 (5 H and 1 H, each s, CMe_2), 3.71 (2 H, s, PhCH_2·CO), 3.92 (3 H, s, CO_2Me), 4.19 (2 H, centre of 2 AB q, *J* 17 Hz, N·CH_2·CO), 4.84 and 4.91 (0.66 H and 0.33 H, each s, N·C*H*·CO_2Me), 7.08 and 7.21 (0.66 H and 0.33 H, each s, N·CH·S), and 7.35br (5 H, s, Ph); *m/e* 348 (M^+), 156 (base peak), and 91 ($C_7H_7^+$ base peak) (Found: C, 58.39; H, 5.93; N, 7.95. Calc. for $C_{17}H_{20}N_2O_4S$: C, 58.62; H, 5.75; N, 8.05%).

(*b*) Experiment (*a*) was repeated except the time of reflux was reduced to 3.5 h. The crude product, obtained after evaporation, was fractionated by silica gel chromatography to give two compounds.

The first-eluted material (0.276 g, 55%) was identical (t.l.c. and n.m.r. spectroscopy) with the penillonate (10a).

The second-eluted material (0.104 g, 28%) was *dimethyl* (3R,4R,7S,12S)-2-*oxo*-3-*phenylacetamido*-6,6,11,11-*tetramethyl*-5,10-*dithia*-1,8-*diazatricyclo*[7.3.0^{4,8}]*dodecane*-7,12-*dicarboxylate* (20a); m.p. 133—135 °C (from Et_2O); $[\alpha]_D$ +218° (0.8% in $CHCl_3$); $\nu_{max.}$ (KBr) 3 315br (NH), 1 742 (ester CO), and 1 685sh and 1 665 cm^{-1} (amide CO); $\lambda_{max.}$ (EtOH) 212 nm (ε 11 200); δ($CDCl_3$) 1.38br, 1.48, and 1.63 (6 H, 3 H, and 3 H, each s, 2 × CMe_2), 3.59 (2 H, s, PhCH_2·CO), 3.70 (6 H, s, 2 × OMe), 4.11 (1 H, s, N·C*H*·CO_2Me), 4.70 (1 H, s, CO·N·C*H*·CO_2Me), 5.03 (1 H, t, $J = J' = 6$ Hz, NH·C*H*·CH), 5.85 (1 H, d, J 6 Hz, CH·C*H*·S), 6.38 (1 H, s, N·CH·S), 6.81 (1 H, d, J 6 Hz, CO·N*H*·CH), and 7.35br (5 H, s, Ph) [addition of D_2O caused the d at 6.81 to disappear and the t at 5.03 to collapse to a d (J 6 Hz)]; *m/e* 521 (M^+) and 91 ($C_7H_7^+$, base peak) (Found: C, 55.22; H, 5.91; N, 8.07%; M^+, 521.168 0. $C_{24}H_{31}N_3O_6S_2$ requires C, 55.28; H, 5.95; N, 8.06%; M, 521.165 4).

(*c*) Experiment (*a*) was repeated except the time of reflux was reduced to 0.5 h. The crude product, obtained after evaporation, was fractionated by silica gel chromatography to give two compounds.

The first-eluted material (0.134 g, 27%) was identical (t.l.c. and n.m.r. spectroscopy) with the penillonate (10a).

The second-eluted material (0.240 g, 64%) was identical (t.l.c. and n.m.r. spectroscopy) with the tricyclododecane (20a).

(*d*) Experiment (*a*) was repeated and after heating under reflux for 4 min the thermolysate was cooled in an ice–water bath. The mixture contained three components (t.l.c.), the R_F values of this coincided with those of the oxazolinone (5),[10] the penillonate (10a), and the tricyclododecane (20a). A portion (5 cm^3) of the thermolysate was evaporated; i.r. spectroscopy revealed that the residue showed the presence of a weak absorption a 1 825 cm^{-1}, a wave number characteristic of the carbonyl group of the oxazolinone (5). The remainder of the thermolysate was treated with benzylamine in dry benzene; evaporation after 2 h, trituration of the residue with benzene, and filtration gave a solid (0.032 g, 9%), m.p. 172—174 °C (from C_6H_6), which was identical (i.r. and mass spectroscopy) with an authentic sample of the benzylamide of *N*-phenylacetylglycine (lit.,[5] m.p. 171—172 °C).

(*e*) Experiment (*a*) was repeated and after heating under reflux for 0.5 h the thermolysate was cooled in an ice–water bath. One half of the mixture was reheated; the other half was evaporated and the residue was dissolved in one equivalent volume of benzene containing 0.01% iodine and the solution was reheated. In each case, the progress of the reaction was monitored by t.l.c. The former reaction was complete in 18 h and the latter reaction in 43 h. Purification of each product by silica gel chromatography afforded a material (*ca.* 70%) which was indistinguishable (t.l.c. and n.m.r. spectroscopy) from the penillonate (10a).

Thermolysis of the Oxazolinone (5) *and the Thiazoline* (8a).—A mixture of the oxazolinone (5) [10] (0.100 g) and the thiazoline (8a) [10] (0.100 g) was heated under reflux in benzene (20 cm^3) containing 0.01% iodine. Formation of the product appeared to be complete within 3 min (t.l.c.). Evaporation and purification of the material by silica gel chromatography gave a substance (0.150 g, 75%) which was identical (t.l.c. and n.m.r. spectroscopy) with the penillonate (10a).

Thermolysis of the Penicillinate (1a) *and the Thiazoline* (8a).—A mixture of the penicillinate (1a) (0.500 g) and the thiazoline (8a) (0.250 g) was heated under reflux in benzene (50 cm^3). After 3.5 h the mixture was evaporated and the product fractionated by silica gel chromatography to give two compounds.

The first-eluted material (0.050 g, 10%) was identical (t.l.c. and n.m.r. spectroscopy) with the penillonate (10a).

The second-eluted material (0.501 g, 66%) was identical (t.l.c. and n.m.r. spectroscopy) with the tricyclododecane (20a).

Thermolysis of the Penicillinate (16).—The 6-epipenicillinate (16) [11] (0.100 g), was heated in benzene (10 cm^3) containing 0.01% iodine for 0.5 h. Evaporation and purification of the product by silica gel chromatography afforded a material (0.050 g, 50%) which was indistinguishable (t.l.c., i.r., n.m.r., and mass spectroscopy) from an authentic sample of methyl benzylpencillenate (18) [12] which had been similarly purified.

Thermolysis of the Penicillinate (16) *and the Thiazoline* (8a).—A mixture of the 6-epipenicillinate (16) (0.200 g) and the thiazoline (8a) (0.100 g) was heated under reflux in benzene (20 cm^3) containing 0.01% iodine for 3.5 h. The product, obtained after evaporation, was purified by silica gel chromatography to give *dimethyl* (3S,4R,7S,12S)-2-*oxo*-3-*phenylacetamido*-6,6,11,11-*tetramethyl*-5,10-*dithia*-1,8-*diazatricyclo*[7.3.0^{4,8}]*dodecane*-7,12-*dicarboxylate* (21) (0.070 g, 23%); m.p. 141—142 °C (from Et_2O); $[\alpha]_D$ +149° (0.78% in $CHCl_3$); $\nu_{max.}$ (KBr) 3 340br (NH), 1 740br (ester CO), and 1 670br cm^{-1} (amide CO); $\lambda_{max.}$ (EtOH) 213 nm (ε 8 700); δ($CDCl_3$) 1.35, 1.44, 1.60, and 1.70 (each 3 H, s, 2 × CMe_2), 3.60 (2 H, s, PhCH_2·CO), 3.73 (6 H, s, 2 × OMe), 3.94 (1 H, s, N·C*H*·CO_2Me), 4.34 (1 H, t, $J = J' = 9$ Hz, NH·C*H*·CH), 4.95 (1 H, s, CO·N·C*H*·CO_2Me), 5.16 (1 H, d, J 9 Hz, CH·C*H*, S), 6.03 (1 H, d, J 9 Hz, CO·N*H*·CH), 6.12 (1 H, s, N·CH·S), and 7.25 (5 H, s, Ph) [irradiation at 6.03 caused the t at 4.34 to collapse to a d (J 9 Hz) and irradiation at 4.34 caused the d at 5.16 and 6.03 to collapse to a s]; *m/e* 521 (M^+) and 174 ($C_7H_{12}NO_2S^+$, base peak) (Found: C, 55.22; H, 5.91; N, 8.07. $C_{24}H_{31}N_3O_6S$ requires C, 55.28; H, 5.95; N, 8.06%).

Thermolysis of the Penicillinate (17).—The 5-epipenicillinate (17) [9] (0.250 g) was heated under reflux in benzene (25 cm^3) containing 0.01% iodine for 0.25 h. Evaporation and fractionation of the product by silica gel chromatography gave two chromatographically homogeneous materials.

The first-eluted material (0.070, 28%) was identical (i.r. and n.m.r. spectroscopy) with the penillonate (10a).

The second-eluted material (0.101 g, 54%) was *dimethyl* (3R,4S,7S,12S)-2-*oxo*-3-*phenylacetamido*-6,6,11,11-*tetramethyl*-5,10-*dithia*-1,8-*diazatricyclo*[7.3.0^{4,8}]*dodecane*-7,12-*dicarboxylate* (22), isolated as a foam; $[\alpha]_D$ +128° (0.76% in $CHCl_3$); $\nu_{max.}$ (film) 3 320br (NH), 1 745 (ester CO), and 1 680br cm^{-1} (amide CO); $\lambda_{max.}$ (EtOH) 225 (ε 8 300); δ(90 MHz, $CDCl_3$) 1.36, 1.43, 1.51, and 1.67 (each 3 H, s, 2 × CMe_2), 3.57 (1 H, s, N·C*H*·CO_2Me), 3.60 (2 H, s, PhCH_2·CO), 3.74 and 3.78 (each 3 H, s, 2 × OMe), 4.47 (1 H, dd, J 8 and J' 10 Hz, NH·C*H*·CH), 5.01 (1 H, s, CO·N·C*H*·CO_2Me), 5.09 (1 H, d, J 10 Hz, CH·C*H*·S), 6.06 (1 H, d, J 8 Hz, CO·N*H*·CH), 6.95 (1 H, s, N·CH·S), and 7.30 (5 H, s, Ph) [irradiation at 4.47 caused the signals at 5.09 and 6.06 to collapse to a s, irradiation at 5.09 caused the signal at 4.47 to collapse to a d (J 8 Hz), and irradiation at 6.06 caused the signal at 4.47 to collapse to a d (J 10 Hz)]; *m/e* 521 (M^+) and 174 ($C_7H_{12}NO_2S^+$, base peak) (Found: M^+, 521.165 5. $C_{24}H_{31}N_3O_6S$ requires M, 521.165 4).

Thermolysis of the Penicillinate (17) *and the Thiazoline* (8a).—A mixture of the 5-epipenicillinate (17) (0.250 g) and the thiazoline (8a) (0.125 g) was heated under reflux in benzene (25 cm^3) containing 0.01% iodine for 0.5 h. Evaporation and purification of the product by silica gel chromatography [C_6H_6–Et_2O (7 : 3) as eluant] afforded a material (0.240 g, 64%) which was identical with the tricyclododecane (22) (n.m.r. spectroscopy).

Thermolysis of the Tricyclododecane (22).—(*a*) The tricyclododecane (22) (0.50 g) was heated under reflux in benzene (50 cm^3) containing 0.01% iodine. Evaporation after 3.5 h and fractionation of the product by silica gel chromatography gave two compounds.

The first-eluted material (0.036 g, 11%) was identical (t.l.c. and n.m.r. spectroscopy) with the penillonate (10a).

The second-eluted compound (0.360 g, 72%) was indistinguishable (t.l.c. and n.m.r. spectroscopy) from the starting material (22).

(*b*) The tricyclododecane (22) (0.200 g) was heated under reflux in benzene (20 cm^3), which had been saturated with hydrogen iodide. Evaporation after 3.5 h and fractionation of the product by silica gel chromatography gave a material (0.090 g, 60%) which was identical (t.l.c. and n.m.r. spectroscopy) with the penillonate (10a).

Thermolysis of the Penillonate (10a) *and the Thiazoline* (8a).—A mixture of the penillonate (10a) (0.200 g) and the thiazoline (8a) (0.100 g) was heated in benzene (20 cm^3) containing 0.01% iodine. Evaporation after 3.5 h gave a residue which was identical (t.l.c. and n.m.r. spectroscopy) to the mixture of starting materials.

Thermolysis of the Oxazolinone (5) *and the Tricyclododecane* (20a).—A mixture of the oxazolinone (5) (0.033 g) and the tricyclododecane (20a) (0.100 g) was heated in benzene (10 cm^3) containing 0.01% iodine for 3.5 h. Evaporation and purification of the product by silica gel chromatography gave the tricyclododecane (20a) (0.072 g, 72%).

Preparation of the Penicillinate (1c).—A mixture of the benzylpenicillinate (1d) (5.58 g, 15 mmol) and triethylamine hydrochloride (2.07 g, 15 mmol) was stirred in dry dichloromethane (60 cm^3). The mixture was then cooled to −78 °C and ethyl chloroformate (4.86 g, 45 mmol) was added. After 1 h, the mixture was washed with sodium hydrogen carbonate solution. Evaporation of the dried ($MgSO_4$) organic layer gave the anhydride (1b) (4.62 g, 76%); δ($CDCl_3$) 1.38 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.52 and 1.58 (each 3 H, s, CMe_2), 3.65 (2 H, s, Ph*CH*$_2$·CO), 4.34 (2 H, q, *J* 7 Hz, MeC*H*$_2$·O), 4.42 (1 H, s, N·C*H*·CO_2), 5.45—5.80 (2 H, m, NH·C*H*·C*H*·S), 6.2br (1 H, d, *J* 8 Hz, CO·N*H*·CH), and 7.28 (5 H, s, Ph).

A solution of the anhydride (1b) (4.50 g) in dry dichloromethane (3 cm^3) was treated with [$^2H_3$]methanol (3.5 g) and a trace of redistilled triethylamine at 28 °C. After 12 h the mixture was diluted with dichloromethane and washed with 1M-hydrochloric acid followed by water. Evaporation of the dried ($MgSO_4$) organic layer gave [$^2H_3$]-*methyl benzylpenicillinate* (1c) (3.15 g, 78%); m.p. 89—90 °C (from Et_2O); $\nu_{max.}$ (KBr) 3 320 (NH), 2 280, 2 200, and 2 100 (CD), 1 785 (β-lactam CO), 1 750 (ester CO), and 1 665 cm^{-1} (amide CO); δ($CDCl_3$) 1.41 and 1.46 (each 3 H, s, CMe_2), 3.58 (2 H, s, PhC*H*$_2$·CO), 4.35 (1 H, s, N·C*H*·CO_2-CD_3), 5.43 (1 H, d, *J* 4 Hz, CH·C*H*·S), 5.52 (1 H, dd, *J* 4 and *J'* 8 Hz, NH·C*H*·CH), 7.02 (1 H, d, *J* 8 Hz, CO·N*H*·CH), and 7.23 (5 H, s, Ph); *m/e* 351 (M^+) and 177 ($C_7H_9D_3NO_2S^+$, base peak) (Found: M^+, 351.132 2. $C_{17}H_{17}D_3N_2O_4S$ requires *M*, 351.133 2).

N.m.r. spectroscopy established that the penicillinate (1c) was >95% trideuteriated.

Thermolysis of the Penicillinate (1c) *and the Thiazoline* (8a).—A mixture of the penicillinate (1c) (0.500 g) and the thiazoline (8a) (0.250 g) was heated under reflux in benzene (50 cm^3) containing 0.01% iodine for 0.75 h. Evaporation and purification of the product by silica gel chromatography gave [$^2H_3$]*methyl* (3R,4R,7S,12S)-12-*methoxycarbonyl*-2-*oxo*-3-*phenylacetamido*-6,6,11,11-*tetramethyl*-5,10-*dithia*-1,8-*diazatricyclo*[7.3.0^{4,8}]*dodecane*-7-*carboxylate* (20b) (0.460 g, 61%), m.p. 135—136 °C (from Et_2O); $\nu_{max.}$ (KBr) 3 310 (NH), 2 270, 2 210, and 2 100 (CD), 1 745 and 1 720 (ester CO), and 1 695 and 1 655 cm^{-1} (amide CO); δ($CDCl_3$) as for compound (20a) except that the signal at 3.70 integrated for 3 H; *m/e* 524 (M^+) and 174 ($C_7H_{12}NO_2S^+$, base peak) (Found: M^+, 524.184 8. $C_{24}H_{28}D_3N_3O_6S_2$ requires *M*, 524.184 2).

N.m.r. spectroscopy indicated that the tricyclododecane (20b) was >95% trideuteriated.

Preparation of the Thiazoline (8b) (*See Ref.* 10).—A solution of the penicillinate (1c) (2.00 g) in trifluoroacetic acid (20 cm^3) was heated on a steam-bath for 0.5 h. The liquid, obtained after evaporation, was purified by short-path distillation (0.05 mmHg at 74 °C) to give [$^2H_3$]*methyl* (4S)-5,5-*dimethylthiazoline*-4-*carboxylate* (8b) (0.600 g, 60%) as a chromatographically homogeneous syrup; $\nu_{max.}$ (film) 2 280, 2 210, and 2 100 (CD), and 1 740 cm^{-1} (ester CO); δ($CDCl_3$) 1.36 and 1.72 (each 3 H, s, CMe_2), 4.60 (1 H, d, *J* 2 Hz, N·C*H*·CO_2CD_3), and 8.09 (1 H, d, *J* 2 Hz, S·C*H*:N) (irradiation at 4.60 caused the d at 8.09 to collapse to a s and *vice versa*); *m/e* 176 (M^+) and 114 (M^+—CO_2CD_3, base peak) (Found: M^+, 176.070 1. $C_7H_8D_3NO_2S$ requires *M*, 176.070 0).

N.m.r. spectroscopy established that the thiazoline (8b) was >95% trideuteriated.

Thermolysis of the Penicillinate (1a) *and the Thiazoline* (8b).—A mixture of the penicillinate (1a) (0.400 g) and the thiazoline (8b) (0.200 g) was heated in benzene (40 cm^3) containing 0.01% iodine for 0.5 h. Evaporation and purification of the product by silica gel chromatography afforded [$^2H_3$]*methyl* (3R,4R,7S,12S)-7-*methoxycarbonyl*-2-*oxo*-3-*phenylacetamido*-6,6,11,11-*tetramethyl*-5,10-*dithia*-1,8-*diazatricyclo*[7.3.0^{4,8}]*dodecane*-12-*carboxylate* (23) (0.310 g, 52%); m.p. 136—137 °C (from Et_2O); $\nu_{max.}$ (KBr) 3 310 (NH), 2 260, 2 180, and 2 080 (CD), 1 740 and 1 720 (ester CO), and 1 695 and 1 655 cm^{-1} (amide CO); δ($CDCl_3$) as for compound (20a) except that the signal at 3.70 integrated for 3 H; *m/e* 524 (M^+) and 177 ($C_7H_9D_3NO_2S^+$, base peak) (Found: M^+, 524.184 8. $C_{24}H_{28}D_3N_3O_6S_2$ requires *M*, 524.184 2).

N.m.r. spectroscopy indicated that the tricyclododecane (23) was >95% trideuteriated.

Thermolysis of the Tricyclododecanes (20b) *and* (23).—(*a*) The tricyclododecane (20b) (0.200 g) was heated in benzene (20 cm^3), which had been saturated with hydrogen iodide, for 3.5 h. Evaporation and purification of the product by silica gel chromatography gave the penillonate (0.080 g, 60%) which was 50% trideuteriated (n.m.r. spectroscopy).

(*b*) The tricyclododecane (23) (0.150 g) was treated as in experiment (*a*) and the crude product was purified by silica gel chromatography. The derived penillonate (0.075 g, 74%) was 52% trideuteriated (n.m.r. spectroscopy).

Preparation of the Penillonate (10b).—The penicillinate (1c) (0.500 g) was heated in benzene containing iodine as described for compound (1a) [experiment (*a*)]. Evapor-

ation and purification of the product as before gave [$^2H_3$]-*methyl benzylpenillonate* (10b) (0.325 g, 65%); m.p. 143—144 °C (from MeOH); $\nu_{max.}$ (KBr) 2 280, 2 200, and 2 100 (CD), 1 752 (ester CO), 1 730 (imidazolidinone CO), and 1 600 cm^{-1} (amide CO); $\delta(CDCl_3)$ as for the penillonate (10a) except for the absence of the signal at 3.92; *m/e* 351 (M^+), 159 (base peak), and 91 ($C_7H_7^+$, base peak) (Found: M^+, 351.1324. $C_{17}H_{17}D_3N_2O_4S$ requires M, 351.133 2).

N.m.r. spectroscopy revealed that the penillonate (19b) was >95% trideuteriated.

Thermolysis of the Penillonate (10b) *and the Thiazoline* (8a).—A mixture of the penillonate (10b) (0.100 g) and the thiazoline (8a) (0.050 g) was heated in benzene (10 cm^3), which had been saturated with hydrogen iodide, for 3.5 h. Evaporation and purification of the product by silica gel chromatography afforded the penillonate (0.062 g, 62%) which was 75% trideuteriated (n.m.r. spectroscopy).

We are grateful to Beecham Pharmaceuticals for a gift of potassium benzylpenicillinate. We also thank Mr. S. Addison for determining the i.r. spectra, Mr. P. Kelly for the mass spectral measurements, Dr. M. N. S. Hill for recording the 90 MHz n.m.r. spectra, and Mr. J. Muers for carrying out the microanalyses.

[9/1615 *Received*, 11*th October*, 1979]

REFERENCES

[1] Part 19, S. D. Carter, A. C. Kaura, and R. J. Stoodley, *J.C.S. Perkin I*, 1980, 388.
[2] 'The Chemistry of Penicillin,' eds. H. T. Clarke, J. R. Johnson, and R. Robinson, Princeton, University Press, 1949, pp. 158 and 188.
[3] Ref. 2, p. 447.
[4] C. W. Bird, *Tetrahedron Letters*, 1964, 609; *Tetrahedron*, 1966, **22**, 2489.
[5] A. B. A. Jansen and R. Robinson, *Monatsch.*, 1967, **98**, 1017.
[6] W. Clegg, *Acta Cryst.*, 1978, **B34**, 3460.
[7] I. McMillan and R. J. Stoodley, *Chem. Comm.*, 1968, 11.
[8] R. Busson and H. Vanderhaeghe, *J. Org. Chem.*, 1976, **41**, 2561.
[9] W. Baker, C. M. Pant, and R. J. Stoodley, *J.C.S. Perkin I*, 1978, 668.
[10] M. R. Bell, J. A. Carlson, and R. Oesterlin, *J. Org. Chem.*, 1972, **37**, 2733.
[11] A. Vlietinck, E. Roets, P. Claes, G. Janssen, and H. Vanderhaeghe, *J.C.S. Perkin I*, 1973, 937.
[12] Ref. 2, pp. 163—164.