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Transformations of Penicillin. Part I. Preparation and Rearrangements of 6β-Phenylacetamidopenicillanic Sulphoxides

By **D. H. R. Barton,* F. Comer, D. G. T. Greig,** and **P. G. Sammes,** Chemistry Department, Imperial College, London SW7
(Mrs.) **C. M. Cooper, G. Hewitt,** and **W. G. E. Underwood,** Glaxo Research Ltd., Greenford, Middlesex

The isomeric sulphoxides of 6β-phenylacetamidopenicillanic acid esters and *N*-t-butyl-amides have been prepared. The (*R*)-sulphoxides can be thermally converted into the (*S*)-isomers. Deuterium labelling showed that the isomerisation proceeds *via* a sulphenic acid intermediate. Rearrangement of the sulphoxides with acetic anhydride produces mainly the corresponding acetoxypenams and acetoxycephams. Both isomers of the acetoxy-substituted penam can be formed by isomerisation of the appropriate sulphoxide.

THE conversion of the penicillins into more active and more β-lactamase-resistant antibiotics is the object of much current research.[1] In 1963 Morin and his co-workers demonstrated the feasibility of converting penicillin sulphoxide esters into deacetoxycephalosporins by an unprecedented acid-catalysed rearrangement.[2] The present paper summarises work aimed at the elucidation of the mechanism of this sulphoxide rearrangement and its application to the preparation of some novel penicillin derivatives.[3]

Oxidation of the penicillanic acid (1; R = H) or its esters with peroxy-acids, hydrogen peroxide, sodium periodate,[4] or even ozone in non-polar solvents [5] gives only one of the two possible sulphoxides.[6] Other reagents tried in the course of our work included *N*-bromosuccinimide [7] and 1-chlorobenzotriazole.[8] Such selectivity suggests either the presence of a powerful directing and stabilising influence during the oxidation or a rapid isomerisation of the initial product into the thermodynamically favoured sulphoxide. Previous studies on the behaviour of different oxidising agents towards sulphides [6] indicate that the former explanation pertains, reagent approach being directed by hydrogen bonding to the side-chain amide proton.[9] Thus the preferred isomer is the (*S*)-isomer (2; $R^1 = PhCH_2$, $R^2 = OMe$), and this result has been substantiated both by an *X*-ray examination of the sulphoxide (2; R^1 =

[1] *Cf.* S. Wolfe, J. C. Godfrey, C. T. Holdrege, and Y. G. Perron, *Canad. J. Chem.*, 1968, **46**, 2549; M. S. Manhas and A. K. Bose, 'Synthesis of Penicillin, Cephalosporin C, and Analogues,' Dekker, New York, 1969, chs. 3, 4.

[2] R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, 1963, **85**, 1896.

[3] During the course of our investigations a full paper on the work by the Lilly group appeared: R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, 1969, **91**, 1401.

[4] D. H. R. Barton, F. Comer, and P. G. Sammes, *J. Amer. Chem. Soc.*, 1969, **91**, 1529.

[5] In protic solvents ozone has been reported to give the less stable sulphoxide: D. O. Spry, *J. Amer. Chem. Soc.*, 1970, **92**, 5006.

[6] *Cf.* C. R. Johnson and D. McCants, jun., *J. Amer. Chem. Soc.*, 1965, **87**, 1109.

[7] R. Harville and S. F. Reed, *J. Org. Chem.*, 1968, **33**, 3976.

[8] W. D. Kingsbury and C. R. Johnson, *Chem. Comm.*, 1969, 365.

[9] H. B. Henbest, *Proc. Chem. Soc.*, 1963, 159; L. Goodman, S. Winstein, and R. Boschan, *J. Amer. Chem. Soc.*, 1958, **80**, 4312.

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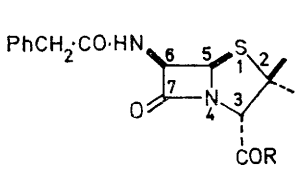
PhO·CH_2, R^2 = OMe) and by detailed ^{1}H n.m.r. studies.[10] As expected, 6β-phthalimidopenam derivatives [*e.g.* (3)], having no side-chain N–H bond, produce mainly the corresponding (*R*)-sulphoxides (4) upon oxidation.[11]

The isomeric (*R*)-sulphoxides of the normal penicillinic series were required for comparison with the (*S*)-sulphoxides. These (*R*)-sulphoxides have recently been obtained both by photo-induced equilibration of (*S*)-sulphoxides [12] and by modified oxidation of sulphides with ozone.[5] An alternative direct approach involves a two-step oxidation *via* sulphonium halide formation; these halides are known to hydrolyse with inversion of configuration.[13] It was considered that chlorination of the methyl ester (1; R = OMe) might form the (*S*)-sulphonium chloride (5) which, upon subsequent hydrolysis with inversion, would give the required (*R*)-sulphoxide (6; R = OMe). This process was effected with either iodobenzene dichloride [14] or t-butyl hypochlorite [15] in aqueous pyridine as oxidant. These oxidations were best performed at low temperatures with only a slight excess of reagent. The reactions were not stereospecific, and both isomeric sulphoxides were formed, although the required (*R*)-sulphoxides were favoured. With an excess of oxidant a new product was also formed. In the methyl ester series use of 3 equiv. of iodobenzene dichloride in aqueous pyridine produced the new product in 18% yield; its analytical figures agreed with the formula $C_{17}H_{18}N_2O_4$. From its mass spectral fragementation pattern, which showed major peaks at *m/e* 160 and 155, and its ^{1}H n.m.r. spectrum, it was shown to be the oxazoline (7). Oxidative removal of the sulphur atom is presumably followed by intramolecular participation of the side chain to form the oxazoline ring. Interestingly, this oxazoline was optically active. Little is known about the mechanism of substitution in four-membered rings and exact details of the mechanism of formation of the oxazoline (7) remains hidden. A similar reaction leading to the oxazoline (7) has been described by Sheehan.[16]



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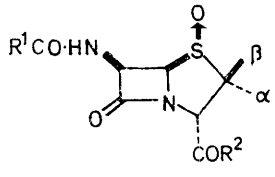

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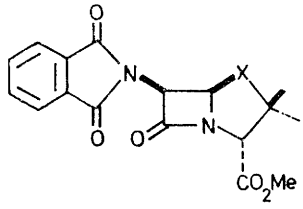
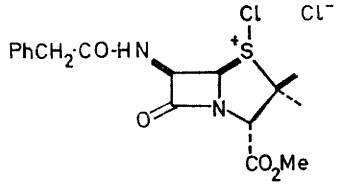


(3) X = S
(4) X = S→O



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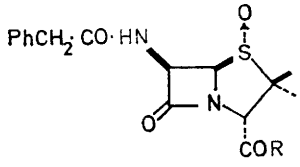

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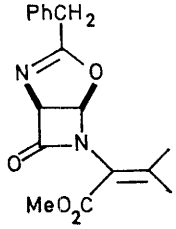

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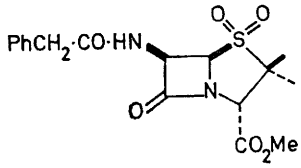

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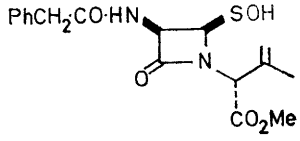

(9)

Oxidation of both the (*R*)- and (*S*)-sulphoxides gives the same sulphone (8).[17a] Furthermore, the (*R*)-sulphoxides are thermally unstable and, in inert solvents, such as refluxing benzene, are rapidly transformed into the more stable (*S*)-sulphoxides.[18] A similar series of reactions was found in our work with the *N*-t-butylamide derivative (6; R = NHBu^t), which gave the (*S*)-sulphoxide (2; R^1 = $PhCH_2$, R^2 = NHBu^t) on heating. This sensitivity of the (*R*)-sulphoxide to heat has precedent in the known thermal instability of certain sulphoxides, and especially in the decomposition of t-alkyl sulphoxides, which proceeds *via* a six-electron sigmatropic process to form sulphenic acids.[19] In the present case this path requires the formation of the sulphenic acid intermediate (9) from the sulphoxide

[10] R. D. G. Cooper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, 1969, **91**, 1408.
[11] R. D. G. Cooper, P. V. DeMarco, and D. O. Spry, *J. Amer. Chem. Soc.*, 1969, **91**, 1528; see also ref. 4.
[12] R. A. Archer and P. V. DeMarco, *J. Amer. Chem. Soc.*, 1969, **91**, 1530.
[13] *Cf.* T. Higuchi, I. H. Pitman, and K. H. Gensch, *J. Amer. Chem. Soc.*, 1966, **88**, 5676; C. R. Johnson, *ibid.*, 1963, **85**, 1020.
[14] G. Barbieri, M. Cinquini, S. Colonna, and F. Montanari; *J. Chem. Soc.* (*C*), 1968, 659.
[15] P. S. Skell and M. F. Epstein, Abstracts of the 147th National Meeting of the American Chemical Society, 1964, p. 26N; see also ref. 6.
[16] J. C. Sheehan in 'Molecular Modifications of Drug Design,' Advances in Chemistry Series, No. 45, American Chemical Society, Washington, D.C., 1964, p. 15.
[17] 'The Chemistry of Penicillin,' eds. H. T. Clarke, J. R. Robinson, and R. Robinson, Princeton University Press, Princeton, New Jersey, 1949, (*a*) p. 177; (*b*) p. 187.
[18] D. H. R. Barton, F. Comer, D. G. T. Greig, G. Lucente, P. G. Sammes, and W. G. E. Underwood, *Chem. Comm.*, 1970, 1059.
[19] J. A. Shelton and K. E. Davis, *J. Amer. Chem. Soc.*, 1967, **89**, 218.

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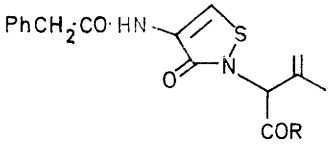
(6; R = OMe). Alternative possibilities, such as pyramidal inversion about the sulphur atom [20] or homolytic scission–recombination mechanisms,[21] were subsequently discounted. The sulphenic acid (9) can either recyclise directly to reform the (*R*)-sulphoxide, or recyclise after rotation about the C(2)–C(3) bond [see (1)] when the more stable (*S*)-sulphoxide (2; R^1 = $PhCH_2$, R^2 = OMe) forms. During the isomerisation the stereospecific *syn*-elimination–addition mechanism only involves the 2α-methyl group, which by a simultaneous rearrangement enters the 2β-position. This process was demonstrated by deuterium labelling. Deuterium exchange of the intermediate sulphenic acid (9) protons occurred when (*R*)-sulphoxide (6; R = OMe) was heated in Bu^tOD.[22] The (*S*)-sulphoxide (2; R^1 = $PhCH_2$, R^2 = OMe) produced contained deuterium. After re-exchanging the side-chain amide proton with methanol, analysis by both ^1H n.m.r. spectroscopy and mass spectroscopy showed that deuterium was specifically incorporated into the 2β-methyl group only. A control experiment, in which the unlabelled (*S*)-sulphoxide was heated under the same conditions, showed negligible deuterium incorporation. It has been reported that prolonged heating of the (*S*)-sulphoxide (2; R^1 = $PhO{\cdot}CH_2$, R^2 = OMe) in benzene containing deuterium oxide is required before deuterium incorporation into the 2β-methyl group is observed.[18] That only *one* deuterium atom is incorporated in our experiment confirms the existence of the sulphenic acid intermediate. Similarly, that only the (*S*)-sulphoxide is formed in the isomerisation, and not an equilibrium mixture, again indicates the presence of a powerful directing influence, probably involving hydrogen bonding of the side chain amide proton to the sulphenic acid intermediate.

The reaction of these sulphenic acid intermediates with acetic anhydride was studied in the hope of introducing acetoxy-groups into the penicillin (or cephalosporin) nucleus.[23] Treatment of the methyl ester (2; R^1 = $PhCH_2$, R^2 = OMe) with acetic anhydride in benzene or toluene at reflux gave several products. The least polar material, isolated by preparative t.l.c., was identified as the isothiazolinone (10; R = OMe), m.p. 150—152°. On heating with pyridine or triethylamine this readily isomerised to the conjugated isomer (11; R = OMe), m.p. 232—233°. These isothiazolinones were identical in their physical properties with material originally isolated by Leonard and Wilson from the chlorination of the compound (12).[24] The proportion of isothiazolinones formed was increased by adding sodium acetate to the mixture. The major product was an inseparable mixture of two acetoxy-compounds, identified as the acetoxy-cepham (13; R = OMe) and -penam (14; R = OMe), in which the latter was predominant. Assignment of configurations was principally based on n.m.r. properties (see Table 1). Also formed was a small quantity of the deacetoxycephalosporin (15; R = Me).



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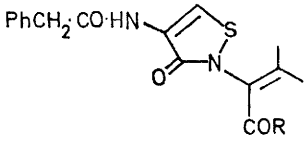

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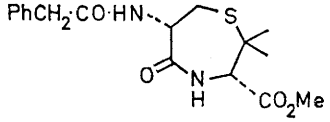

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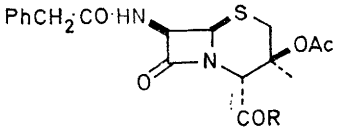

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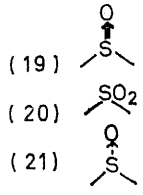

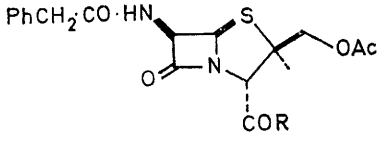

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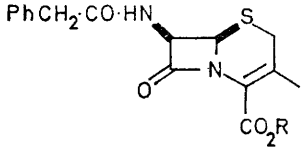

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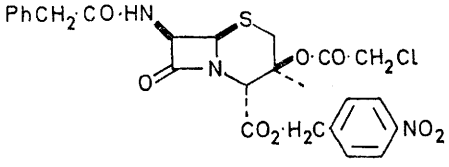

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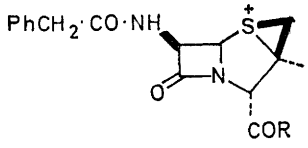

(17)

[20] K. Mislow, *Rec. Chem. Progr.*, 1967, **28**, 217; D. R. Rayner, E. G. Miller, P. Bickart, A. J. Gordon, and K. Mislow, *J. Amer. Chem. Soc.*, 1966, **88**, 3138.

[21] C. A. Kingsbury and D. J. Cram, *J. Amer. Chem. Soc.*, 1960, **82**, 1810.

[22] M. Morton, J. A. Cala, and J. Dissma, *J. Amer. Chem. Soc.*, 1956, **78**, 5394.

[23] R. J. Stedman, K. Swered, and J. R. E. Hoover, *J. Medicin. Chem.*, 1964, **7**, 117.

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

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Again the proportion of this compound was increased by the presence of small amounts of sodium acetate in the reaction mixture.

Because of the difficulty in separating the two acetoxy-components in the methyl series, other ester derivatives were also investigated. The trichloroethyl derivative (2; $R^1 = PhCH_2$, $R^2 = O{\cdot}CH_2{\cdot}CCl_3$) gave products similar to those obtained with the methyl ester, but the two acetoxy-derivatives, the penam (14; $R = O{\cdot}CH_2{\cdot}CCl_3$) and the cepham (13; $R = O{\cdot}CH_2{\cdot}CCl_3$), could be readily separated by careful t.l.c. Again the penam derivative was the major product. The *p*-nitrobenzyl ester (2; $R^1 = PhCH_2$, $R^2 = p\text{-}O_2N{\cdot}C_6H_4{\cdot}CH_2{\cdot}O$) gave similar results, but with acetic anhydride alone much less of the cepham compound (13; $R = p\text{-}O_2N{\cdot}C_6H_4{\cdot}CH_2{\cdot}O$) was formed and only the penam derivative was isolated. Isolation of the latter material was facilitated by using shorter reaction times with lower overall conversion of starting material. Since little of the cepham was formed with the *p*-nitrobenzyl ester, rearrangement of the sulphoxide (2; $R^1 = PhCH_2$, $R^2 = p\text{-}O_2N{\cdot}C_6H_4{\cdot}CH_2{\cdot}O$) with chloroacetic anhydride was attempted. In contrast to the result with acetic anhydride only the chloroacetoxycepham (16) was formed. This implies that the direction of opening of the sulphonium intermediate, such as (17), depends on the strength of the acid used; weak acids, with strong conjugate anions, favour the formation of penams, and strong acids, with weak conjugate bases, prefer the formation of cephams. Recently it has been shown that toluene-*p*-sulphonic acid anhydrides also give mainly cepham products.[25] The penams are thus the kinetic products of opening of the sulphonium ion and the cephams the thermodynamic products.

A related series of reactions with the *N*-t-butylamide derivative (2; $R^1 = PhCH_2$, $R^2 = NHBu^t$) was also investigated, since it was originally felt that in this case the enolisability of the 3β-proton would be lowered, thus favouring quenching of the sulphonium intermediate by external nucleophiles, such as acetate ions, rather than by elimination of the 3β-proton. In fact, by use of acetic anhydride–toluene mixtures, good yields of the desired acetoxy-derivatives were formed, with little isothiazolinone formation. The acetoxycepham (13; $R = NHBu^t$) crystallised directly from the reaction mixture, whereas the penam (14; $R = NHBu^t$) could be isolated but only as a non-crystalline solid. A correlation between the crystalline product and the corresponding trichloroethyl ester (13; $R = O{\cdot}CH_2{\cdot}CCl_3$) was made chemically. Treatment of the latter ester with zinc dust in aqueous acetic acid [26] gave the free acid, which was converted directly into the t-butylamide.

TABLE 1

^{1}H N.m.r. data [a]

Compound	α-Me	β-Me	AcO·CH$_2$ [b]	CH$_2$·S [b]	3-H	4-H	5-H	6-H	7-H
(1; R = OMe)	8·55	8·55			5·61		4·47d (4)	4·39dd (4·11)	
(2; R^1 = PhCH$_2$, R^2 = OMe)	8·83	8·35			5·43		5·08d (4)	4·05dd (4·10)	
(6; R = OMe)	8·41	8·76			5·76		5·38d (4)	4·79dd (4·7)	
(13; R = NHBu^t)	8·45			6·25, 6·80 (14)		5·51		4·70d (4·5)	4·42dd (4·5, 9)
(19; R = NHBu^t)	8·42			5·67, 6·65 (15)		5·40		5·03d (4·5)	4·00dd (4·5, 9)
(21; R = NHBu^t)	8·35			6·20, 6·70 (14)		5·10		5·16d (4·5)	4·73dd (4·5, 8)
(20; R = NHBu^t)	8·33			5·93, 6·10 (14)		5·56		4·86d (4·5)	4·01dd (4·5, 10)
(14; R = O·CH$_2$·CCl$_3$)	8·48		5·67, 6·32 (12)		5·25		4·41d (4)	4·32dd (4·11)	
(22; R = O·CH$_2$·CCl$_3$)	8·62		5·40		5·25		5·21d (4)	5·82dd (4·11)	
(23; R = O·CH$_2$·CCl$_3$)		8·30	5·43, 6·02 (12·5)		5·20		4·98d (4)	3·94dd (4·9)	
(24; R = O·CH$_2$·CCl$_3$)	8·73		5·26, 5·52 (12)		5·18		5·05d (4)	3·99dd (4·9)	

[a] See Experimental section for details; τ values; *J* (Hz) in parentheses. [b] AB quartets. Where split the midpoints of signals were taken without correction.

The acetoxypenams and cephams are isomeric and difficult to distinguish from one another, but this could be done by a careful comparison of their physical properties. The acetoxycephams have a lower β-lactam carbonyl absorption in the i.r. region than the acetoxypenams, the former absorbing at 1760—1775 and the latter at 1780—1795 cm.$^{-1}$. Specific optical rotations of the cephams (generally $<50°$) also appeared to be consistently lower than those for the penams (generally $>100°$). More convincing correlations were obtained from ^{1}H n.m.r. measurements (Table 1). The chemical shifts of the methylene protons in the groups CH$_2$·OAc and S·CH$_2$ differ, the latter resonances being *ca.* 0·5 p.p.m. to higher field. Also, whereas the coupling constant for the former AB quartet is *ca.* 12 Hz, that for

[25] C. J. Daniels, J. W. Fisher, B. J. Foster, J. E. Gutowski, and L. D. Hatfield, personal communication.

[26] *Cf.* T. B. Windholz and D. B. R. Johnston, *Tetrahedron Letters*, 1967, 2555.

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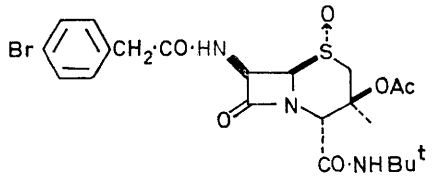
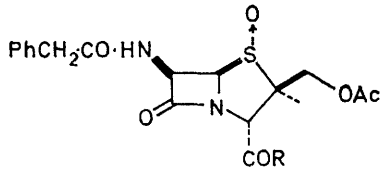
the S·CH_2 quartet is *ca.* 14 Hz.[27] A long range coupling of *ca.* 1 Hz was apparent in the acetoxycephams between the proton at position 4 and one of the geminal protons at position 2. Such coupling is generally observed when the protons and the intervening carbon atoms lie as a planar **W**.[28] Examination of Dreiding models confirms that this is only possible in the case of the cepham. The constitution of the two series was further confirmed by the use of nuclear Overhauser effects.[29]

In order to provide additional, conclusive evidence for the structure of the cepham compounds, an *X*-ray study of the cepham sulphoxide (**18**), prepared from 6β-(*p*-bromophenyl)acetamidopenicillanic acid (see Experimental section) confirmed the assigned structure.[30]

penams (**14**). Oxidation of the trichloroethyl ester (**14**; R = O·CH_2·CCl_2) with iodobenzene dichloride gave two sulphoxides, the required acetoxy-(*R*)-sulphoxide (**22**; R = O·CH_2·CCl_3) and its isomer (**24**; R = O·CH_2·CCl_3), both as non-crystalline solids. Heating the (*R*)-sulphoxide (**24**; R = O·CH_2·CCl_3) in toluene rapidly afforded a new, isomeric sulphoxide, shown by its ^{1}H n.m.r. properties to be the compound (**23**; R = O·CH_2·CCl_3). These reactions were repeated in the *p*-nitrobenzyl ester series, the sulphide (**14**; R = *p*-O_2N·C_6H_4·CH_2·O) giving the two sulphoxides (**22**; R = *p*-O_2N·C_6H_4·CH_2·O) and (**24**; R = *p*-O_2N·C_6H_4·CH_2·O) with either iodobenzene dichloride or t-butyl hypochlorite in aqueous pyridine. With



(18)



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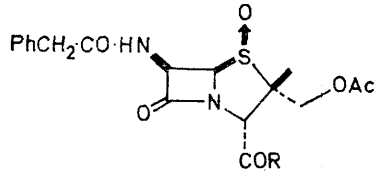
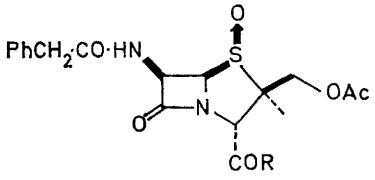


(23)



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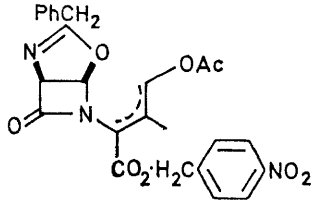

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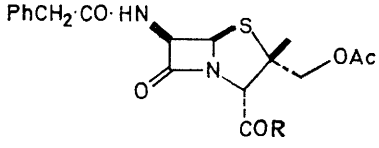

(26)

The oxidation of the acetoxycephams deserves comment. In contrast to oxidation of the penam derivatives,[31] the direction of sulphoxide formation from the t-butyl-amide (**13**; R = NHBu^t) depended on the oxidant used. Monoperphthalic acid gave mainly the (*S*)-sulphoxide (**19**) and, on overoxidation, the corresponding sulphone (**20**). With sodium periodate the principal product was the (*R*)-sulphoxide (**21**), further oxidation of which also gave the sulphone (**20**). The direction of oxidation in this series thus depends on the nature of the oxidant far more than in the unsubstituted penam series.

One further series of acetoxy-substituted penicillinic compounds has also been prepared. Since during the isomerisation of the penicillin (*R*)-sulphoxides into the (*S*)-isomers, rotation about the C(2)–C(3) bond must occur, any substituents on the 2β-methyl group would end up in the 2α-methyl position [*e.g.* (**22**) ⟶ (**23**)]. This concept was applied to the 2β-acetoxy-substituted

excess of oxidant another compound was formed. This was shown to be a mixture of the conjugated and non-conjugated oxazolines (**25**), having similar physical properties to the simpler oxazoline (**7**).

Heating the (*R*)-sulphoxide (**22**; R = *p*-O_2N·C_6H_4·CH_2·O) in toluene again caused isomerisation into the new sulphoxide (**23**; R = *p*-O_2N·C_6H_4·CH_2·O). Reduction of the latter sulphoxide with phosphorus tribromide in dimethylformamide at 0° for 10 min. gave the 2α-acetoxymethylpenam (**26**; R = *p*-O_2N·C_6H_4·CH_2·O) as a non-crystalline foam. Direct hydrogenolysis of this product gave the corresponding acid (**26**; R = OH), isolated as its sodium salt trihydrate, exemplifying a new series of substituted penicillins.[32]

The minimum inhibitory concentration of this penicillin against representative *Staphyllococcus* species and corresponding data for penicillin G (**1**; R = OH)

[27] R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron*, 1966, Suppl. 7, p. 355.
[28] J. M. Lehn, A. Rassat, C. W. Jefford, and B. Waegell, *Tetrahedron Letters*, 1964, 233; M. Barfield, *J. Chem. Phys.*, 1964, **41**, 3825.
[29] F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, 1965, **87**, 5250; see also ref. 10.
[30] M. L. Smart and D. Rogers, *Chem. Comm.*, 1970, 1060.
[31] *Cf.* G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and F. M. van Heyningen, *J. Org. Chem.*, 1970, **35**, 2430.
[32] D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *Chem. Comm.*, 1970, 1683. *Cf.* D. O. Spry, *J. Amer. Chem. Soc.*, 1970, **92**, 5006.

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and the 2β-acetoxymethylpenam (14; R = OH) are given in Table 2.

TABLE 2

Minimum inhibitory concentrations (μg./ml.) against *Staphyllococcus* strains

Strain:	663	3452	11,127
(26; R = OH) *	0·16	125	31
(14; R = OH) *	0·3	125	125
(1; R = OH) *	0·005	250	125

* As sodium salt.

EXPERIMENTAL

I.r. spectra were recorded with a Unicam SP 200 spectrometer for Nujol mulls, unless otherwise stated, and u.v. spectra with a Unicam SP 800 spectrometer for ethanolic solutions. Mass spectra were determined with an A.E.I. MS9 machine, important peaks being assigned by accurate mass measurements. ^{1}H N.m.r. spectra were recorded with either a Varian A60 or HA100 instrument for solutions in deuteriochloroform containing tetramethylsilane as internal reference. Reactions were monitored by t.l.c. on Merck silica gel GF_{254} with acetone–benzene and ethyl acetate–benzene as solvents. Light petroleum refers to the fraction of boiling range 60—80°. M.p.s were determined with a Kofler hot-stage apparatus.

(1S)-6β-*Phenylacetamidopenicillanic Acid* 1-*Oxide* (2; R^1 = $PhCH_2$, R^2 = OH).—Sodium 6β-phenylacetamidopenicillanate (14·2 g.) in water (300 ml.) and phosphate buffer (pH 6·8; 0·2M; 80 ml.) was stirred with a solution of sodium periodate (10·0 g.) in water (300 ml.) at room temperature for 3 hr. The mixture was acidified to pH 2 with phosphoric acid (20% v/v) and extracted with ethyl acetate (400 ml.). The organic layer was washed with water, dried, and evaporated *in vacuo* at *ca.* 25° until the onset of crystallisation; the solution was then cooled to 0° for 5—10 min. The sulphoxide acid isolated (11·6 g.) was sufficiently pure for subsequent reactions. A sample recrystallised from ethyl acetate had m.p. 160—163° (decomp.) [lit.,[33] 142—143° (decomp.)], $[\alpha]_D^{25}$ +235° (*c* 1 in $CHCl_3$), $\nu_{max.}$ 3380, 1785, 1700, 1525, and 1020 cm.$^{-1}$, τ 1·46 (1H, s, CO_2H), 2·76 (5H, m, Ph), 4·00br (2H, s), 5·00 (1H, d, *J* 5 Hz, H-5), 5·40 (1H, s, H-3), 6·40 (2H, s, CH_2Ph), 8·30 (3H, s), and 8·75 (3H, s).

Methylation of the acid (1·0 g.) with an excess of diazomethane in ether–dichloromethane (1 : 3) at room temperature rapidly afforded the methyl ester (2; R^1 = $PhCH_2$, R^2 = MeO) (0·9 g.), m.p. 124—126° (lit.,[17b] 123°), $[\alpha]_D^{20}$ +262° (*c* 1·1 in dioxan), $\nu_{max.}$ 3350, 1780, 1740, and 1670 cm.$^{-1}$, τ 2·76 (5H, m, Ph), 2·94 (1H, d, *J* 10 Hz, NH), 4·05 (1H, dd, *J* 4 and 10 Hz, H-6), 5·08 (1H, d, *J* 4 Hz, H-5), 5·43 (1H, s, H-3), 6·26 (3H, s, MeO), 6·47 (2H, s, CH_2Ph), 8·35 (3H, s), and 8·83 (3H, s).

(1S)-2,2-*Dimethyl*-6β-*phenylacetamido*-3-*t*-*butylcarbamoylpenam* 1-*Oxide* (2; R^1 = $PhCH_2$, R^2 = $NHBu^t$).—The acid (2; R^1 = $PhCH_2$, R^2 = OH) (6·3 g.) in dichloromethane (600 ml.) at 0° (ice-bath) was treated successively with triethylamine (2·0 ml.) and ethyl chloroformate (1·6 ml.). After 30 min. at 0°, t-butylamine (2·1 ml.; freshly redistilled) was added and the solution was allowed to warm to room temperature during 1 hr. It was then washed with 0·5N-hydrochloric acid and water, dried, and evaporated *in vacuo* to give the *t-butyl-amide*. A sample crystallised from dichloromethane gave prisms, m.p. 165—167° (decomp.), $[\alpha]_D^{22}$ +197° (*c* 0·9 in $CHCl_3$), $\nu_{max.}$ 3300, 1785, 1695, 1670, 1550, 1525, and 1018 cm.$^{-1}$, τ 2·70 (5H, m, Ph) 3·52br (1H, s, NH), 4·01 (1H, dd, *J* 5 and 10 Hz, 6-H), 5·08 (1H, d, *J* 5 Hz, 5-H), 5·60 (1H, s, 3-H), 6·42 (2H, s, CH_2Ph), 8·26 (3H, s, Me), 8·80 (3H, s, Me), and 8·65 (9H, s, Bu^t) (Found: C, 59·0; H, 6·6; N, 10·9; S, 7·7. $C_{20}H_{27}N_3O_4S$ requires C, 59·2; H, 6·7; N, 10·4; S, 7·9%).

p-*Nitrobenzyl* 6β-*Phenylacetamidopenicillanate* 1-*Oxide* (2; R^1 = $PhCH_2$, R^2 = p-$O_2N{\cdot}C_6H_4{\cdot}CH_2{\cdot}O$).—The acid (2; R^1 = $PhCH_2$, R^2 = OH) (2 g.), triethylamine (0·8 ml.), and *p*-nitrobenzyl bromide (1·26 g.) in *NN*-dimethylformamide (30 ml.) were stirred at room temperature for 2·5 hr. The solution was poured into iced water (150 ml.) and the mixture was extracted with ethyl acetate (2 × 50 ml.). The extracts were washed with saturated aqueous sodium hydrogen carbonate and water, and dried. Evaporation afforded the *ester* as a pale yellow solid (2·36 g., 85%). Recrystallised from ethyl acetate–light petroleum this had m.p. 142—144°, $[\alpha]_D^{20}$ +165° (*c* 1 in $CHCl_3$) $\lambda_{max.}$ 265 nm. (ε 13,800), $\nu_{max.}$ 3350, 1780, 1742, 1686, and 1512 cm.$^{-1}$, τ 1·71 and 2·41 (4H, m, *p*-nitrophenyl), 2·70 (5H, m, Ph), 2·89 (1H, d, *J* 10 Hz, NH), 3·95 (1H, dd, *J* 5 and 10 Hz, 6-H), 4·67 (2H, s, $CO_2{\cdot}CH_2$), 5·00 (1H, d, *J* 5 Hz, 5-H), 5·30 (1H, s, 3-H), 6·42 (2H, s, CH_2Ph), 8·33 (3H, s), and 8·87 (3H, s) (Found: C, 56·9; H, 4·7; N, 8·7; S, 6·2. $C_{23}H_{23}N_3O_7S$ requires C, 56·9; H, 4·8; N, 8·7; S, 6·6%).

Oxidation of Methyl 6β-*Phenylacetamidopenicillanate with Iodobenzene Dichloride*.—To the ester (1; R = OMe) (342 mg.) in pyridine (8 ml.) containing water (1 ml.) at −10° a solution of iodobenzene dichloride (0·8 g., 3 equiv.) in pyridine (8 ml.) was added dropwise during 10 min. The solution was left at −10° for a further 1·5 hr. before being poured into ethyl acetate (50 ml.). The organic phase was washed with 2N-sulphuric acid and water, dried, and evaporated to give a yellow oil. Preparative t.l.c. (silica gel; 1 : 3 acetone–benzene) afforded three fractions. The least polar material (R_F 0·5) (56 mg.) was the oxazoline. This crystallised from ether as needles of *methyl* 2-(3-*benzyl* 7-*oxo*-4-*oxa*-2,6-*diazabicyclo*[3,2,0]*hept*-2-*en*-6-*yl*)-3-*methylbut*-2-*enoate* (7), m.p. 123°, $[\alpha]_D^{25}$ +65° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ 1760, 1710, 1650, and 1620 cm.$^{-1}$, τ 2·73 (5H, m, Ph), 4·05 (1H, d, *J* 4 Hz, 5-H), 4·83 (1H, d, *J* 4 Hz, 1-H), 6·28 (3H, s, MeO), and 6·33 (2H, s, CH_2Ph), *m/e* 314 (2%), 283 (3), 255 (1), 160 (100), 159 (55), 155 (42), 140 (10), 127 (15), and 91 (82) (Found: C, 64·7; H, 5·8; N, 9·0; S, 0·0%; *M*$^+$, 314·1258. $C_{17}H_{18}N_2O_4$ requires C, 65·0; H, 5·8; N, 8·9; S, 0·0%; *M*, 314·1266).

The next fraction (R_F 0·4) (111 mg.) proved to be the (*S*)-sulphoxide (2; R^1 = $PhCH_2$, R^2 = MeO), and the most polar material (R_F 0·2) (106 mg.) was the (*R*)-sulphoxide (6; R = OMe). Crystallisation from ether–acetone gave *methyl* (1R)-6β-*phenylacetamidopenicillanate* 1-*oxide*, m.p. 124—125°, $[\alpha]_D^{26}$ +176° (*c* 1·0 in $CHCl_3$), $[\alpha]_D^{23}$ +208° (*c* 1·0 in dioxan), $\nu_{max.}$ 3250, 1790, 1748, 1226, and 1070 cm.$^{-1}$, τ 2·71 (5H, m, Ph), 3·39 (1H, d, *J* 7 Hz, NH), 4·79 (1H, dd, *J* 4 and 7 Hz, 6-H), 5·38 (1H, d, *J* 4 Hz, 5-H), 5·67 (1H, s, 3-H), 6·20 (3H, s, MeO), 6·37 (2H, s, $PhCH_2$), 8·41 (3H, s, 2α-Me), and 8·76 (3H, s, 2β-Me) (Found: C, 56·0; H, 5·7; N, 7·7; S, 9·7. $C_{17}H_{20}N_2O_5S$ requires C, 56·0; H, 5·5; N, 7·7; S, 9·5%).

A similar oxidation with only 2 equiv. of iodobenzene dichloride and the methyl ester (696 mg.) gave the (*R*)-sulphoxide (6; R = MeO) (340 mg., 48%), m.p. (from ethyl

[33] A. W. Chow, N. M. Hall, and J. R. E. Hoover, *J. Org. Chem.*, 1962, **27**, 1381.

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acetate) 124—125°, together with very little oxazoline and the (*S*)-sulphoxide (2; R^1 = $PhCH_2$, R^2 = MeO) (140 mg., 20%).

Methyl 6β-Phenylacetamidopenicillanate 1,1-Dioxide (8).[22]—The methyl ester (1; R = OMe) (100 mg.) was oxidised with potassium permanganate (0·2M; 4 ml.) in dioxan (10 ml.) containing phosphate buffer (5 ml.; pH 6·8). After 1 hr. at room temperature the solution was decolourised with sulphur dioxide and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness. The crystalline residue afforded the sulphone (8) (65 mg.), m.p. (from chloroform–ether) 173—175°, $[\alpha]_D^{25}$ +169° (*c* 1 in $CHCl_3$). A similar oxidation of both the (*S*)-sulphoxide (2; R^1 = $PhCH_2$, R^2 = MeO) and the (*R*)-isomer (6; R = OMe) afforded the same sulphone, with identical m.p., mixed m.p., and t.l.c. properties.

2,2-*Dimethyl*-6β-*phenylacetamido*-3-*t*-*butylcarbamoylpenam* (1; R = $NHBu^t$).—Sodium 6β-phenylacetamidopenicillanate (356 mg.) in chloroform (100 ml.) was stirred with triethylamine (0·153 ml.) and ethyl chloroformate (0·100 ml.) at 0° for 30 min. t-Butylamine (0·115 ml.) was added, and the solution was stirred at room temperature for a further 1 hr., washed with water, 0·05N-hydrochloric acid, and water, and evaporated *in vacuo* to give the *t-butylamide* (340 mg.). Crystallised from methylene chloride as prisms, this had m.p. 193—196° (decomp.), $[\alpha]_D^{23}$ +207° (*c* 0·8 in $CHCl_3$), $\nu_{max.}$ 3370, 3330, 1775, 1690, 1660, 1550, and 1530 $cm.^{-1}$, τ 2·96br (5H, s, Ph), 3·52 (1H, d, *J* 9 Hz, NH), 3·67 (1H, s, NH), 4·29 (1H, dd, *J* 4 and 9 Hz, 6-H), 4·65 (1H, d, *J* 4 Hz, 5-H), 5·95 (1H, s, 3-H), 6·40 (2H, s, CH_2Ph), 8·37 (3H, s), 8·49 (3H, s), and 8·65 (9H, s) (Found: C, 61·6; H, 6·9; N, 10·75; S, 8·5. $C_{20}H_{27}N_3O_3S$ requires C, 61·7; H, 7·0; N, 10·6; S, 8·2%).

(1R)-2,2-*Dimethyl*-6β-*phenylacetamido*-3-*t*-*butylcarbamoylpenam* 1-*Oxide* (6; R = $NHBu^t$).—To the amide (1; R = $NHBu^t$) (300 mg.) in pyridine (5 ml.) and water (0·5 ml.) at −30° was added iodobenzene dichloride (280 mg.). The product was worked up as described for the methyl ester. Purification by preparative t.l.c. gave, as the less polar material, the (*S*)-sulphoxide (2; R^1 = $PhCH_2$, R^2 = $NHBu^t$) (42 mg.). The more polar product, obtained as a non-crystalline foam, was the (R)-*sulphoxide*, $[\alpha]_D^{22}$ +142° (*c* 0·8 in $CHCl_3$), $\nu_{max.}$ 3300, 1780, 1695, 1670, 1550, 1525, and 1020 $cm.^{-1}$, τ 2·74 (5H, m, Ph), 3·5 (1H, d, *J* 9 Hz, NH), 4·80 (1H, dd, *J* 4·5 and 9 Hz, 6-H), 5·40 (1H, d, *J* 4·5 Hz), 5·85 (1H, s, 3-H), 6·45 (2H, s, $PhCH_2$), 8·44 (3H, s), and 8·65br (1H, s) (Found: C, 59·3; H. 6·65; N, 10·15; S, 8·0. $C_{20}H_{27}N_3O_4S$ requires C, 59·2; H, 6·7; N, 10·4; S, 7·9%).

Isomerisation of the (R)-*Sulphoxides*.—The methyl ester (6; R = OMe) (100 mg.) was heated in dry toluene (40 ml.) at reflux under oxygen-free nitrogen for 30 min. The solvent was removed *in vacuo* and the residue was purified by column chromatography (silica gel; 1 : 2 ethyl acetate–benzene) to give the crystalline (*S*)-sulphoxide (2; R^1 = $PhCH_2$, R^2 = MeO) (78 mg.) identical (in m.p., mixed m.p., i.r. and n.m.r.) with that already described.

In a similar way the t-butylamide (6; R = $NHBu^t$) (20 mg.) was heated in dry toluene at reflux for 30 min. to give, by preparative t.l.c. (silica gel; 1 : 2 ethyl acetate–benzene), the (*S*)-sulphoxide (2; R^1 = $PhCH_2$, R^2 = $NHBu^t$) (10 mg.), identical (m.p. mixed m.p., i.r., and t.l.c.) with the material already described.

* We thank Dr. G. Lucente for checking these results.

Incorporation of Deuterium.*—(*a*) The methyl ester (6; R = OMe) (284 mg.) was heated in refluxing benzene (5 ml. containing t-butyl [^{2}H]alcohol (1·1 ml.; ^{1}H n.m.r. assay >95%) for 3 hr. The residue obtained after removal of solvents was dissolved in methanol, and the solution was set aside for 16 hr. at room temperature. Preparative t.l.c. of the product (5 : 95 acetone–benzene; ×3) gave the corresponding (*S*)-sulphoxide (110 mg.), and unchanged (*R*)-sulphoxide (40 mg.). The (*S*)-sulphoxide showed, in its integrated ^{1}H n.m.r. spectrum a ratio of the two methyl signals (2β : 2α) of 2·54 : 3·00, indicating an incorporation of 46% deuterium; the amide proton integrated as 1·01H. The recovered (*R*)-sulphoxide showed no deuterium incorporation.

(*b*) The methyl ester (6; R = OMe) (273 mg.) was heated in refluxing t-butyl [^{2}H]alcohol (3 ml.) for 3 hr. Purification of the product as in (*a*) gave the (*S*)-sulphoxide (41 mg.) with a ^{1}H n.m.r. methyl ratio (2β : 2α at τ 8·28 and 8·86) of 2·40 : 3·00, indicating a 60% incorporation of deuterium. In its mass spectrum this material showed peaks due to the molecular ion at *m/e* 364 (M^+) (55%), 365 (M + 1; 100%), 366 (M + 2; 32%), and 367 (M + 3; 10%). An undeuterated sample showed peaks at *m/e* 364 (M^+; 100%), 365 (M + 1; 33%), 366 (M + 2; 10%), and 367 (M + 3; 2%).

(*c*) The (*S*)-sulphoxide (2; R^1 = $PhCH_2$, R^2 = OMe) (100 mg.) was heated in refluxing t-butyl [^{2}H]alcohol for 3 hr. Work-up then gave a virtually quantitative recovery of starting material. After re-exchanging the side chain NH proton with methanol, the methyl ratio was 2·98 : 3·00. The msss spectrum was identical with that of starting material, indicating no detectable deuterium incorporation.

Reaction of the Methyl Ester (S)-*Sulphoxide* (2; R^1 = $PhCH_2$, R^2 = OMe) *with Acetic Anhydride*.—The ester (364 mg.) was heated in refluxing benzene (25 ml.) containing acetic anhydride (5 ml.) for 21 hr. The solvent was then removed *in vacuo* and the traces of acetic anhydride remaining were removed by adding toluene (5 ml.) and re-evaporating to dryness. The residual non-crystalline foam was separated by preparative t.l.c. (1 : 3 acetone–benzene as solvent). The principal product was eluted with acetone to give, as a non-crystalline mixture, methyl 2β-acetoxymethyl-2α-methyl-6β-phenylacetamidopenam-3α-carboxylate (14; R = OMe) and methyl 3β-acetoxy-3α-methyl-7β-phenylacetamidocepham-3α-carboxylate (13; R = OMe) (total 230 mg.). Attempts to separate the mixture with a variety of solvent systems all failed. On the basis of the ^{1}H n.m.r. spectrum the ratio of components was estimated to be *ca.* 2 : 1 in favour of the penam isomer. On adding ether (10 ml.) to the mixture the product all dissolved but white needles were slowly deposited. These were methyl 3-methyl-7β-phenylacetamidoceph-3-em-4-carboxylate (15; R = Me) (16 mg.), m.p. (from ethyl acetate–ether) 187—188°, $[\alpha]_D^{25}$ +86·5° (*c* 1 in $CHCl_3$), $\lambda_{max.}$ 265 nm (ε 6900), $\nu_{max.}$ ($CHCl_3$), 3410, 1780, 1720, 1680, and 1640 $cm.^{-1}$, τ 2·68 (5H, Ph), 3·65 (1H, d, NH, *J* 9 Hz), 4·23 (1H, dd, *J* 4·9 Hz, 7-H), 5·04 (1H, d, *J* 4 Hz, 6-H), 6·20 (3H, s, MeO), 6·38 (2H, s, CH_2Ph), 6·66 and 6·78 (2H, CH_2·S), and 7·91 (3H, s, Me) (Found: C, 58·8; H, 5·2; N, 8·1; S, 9·15. $C_{17}H_{18}N_2O_4S$ requires C, 59·0; H, 5·2; N, 8·1; S, 9·3%), identical with the compound obtained from the parent acid [23] by methylation with diazomethane.

Another product from the rearrangement ran a little faster than the major product on preparative t.l.c. This material was eluted with acetone to give, after removal of

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the solvent, crystalline methyl 3-methyl-2-(3-oxo-4-phenylacetamido-Δ^4-isothiazolin-2-yl)but-3-enoate (10; R = OMe) (23 mg.), m.p. (from ethanol) 149—151° (lit.,[25] 150—152°), $\nu_{max.}$ 3300, 1740, 1680, 1625, 1580, and 1520 cm.$^{-1}$, $[\alpha]_D^{26}$ −38° (*c* 1·0, $CHCl_3$), $\lambda_{max.}$ 295 nm (ε 10,500), τ 1·40 (1H, s, 5-H), 1·70 (1H, s, NH), 2·54 (5H, m, Ph), 4·41 (1H, s, CH·CO_2), 4·75 and 4·94 (2H, CH_2=C), 6·27 (5H, s, PhC*H*$_2$ and MeO), and 8·20 (3H, s, Me).

On treatment with a few drops of triethylamine in chloroform at room temperature this isomer rearranged into the conjugated derivative (11; R = OMe), m.p. (from ethanol), 230—233°, (lit.,[25] 232—233°), $\lambda_{max.}$ 295 nm (ε 10,000), $\nu_{max.}$ 3300, 1710, 1680, 1620, 1580, and 1520 cm.$^{-1}$, τ 1·30 (3H, s, 5H), 1·40 (1H, s, NH), 2·64 (5H, m, Ph), 6·22 (2H, s, C*H*$_2$Ph), 6·30 (3H, s, MeO), 7·70 (3H, s, Me), and 8·14 (3H, s, Me).

Rearrangement of the Trichloroethyl Ester (2; R^1 = $PhCH_2$, R^2 = O·CH_2·CCl_3).—The ester (10 g.) was heated in refluxing toluene (300 ml.) and acetic anhydride (200 ml.) under dry nitrogen for 25 hr.; no starting material then remained. The solvent was removed *in vacuo*, the residue was extracted with ethyl acetate, and the solution was washed with saturated sodium hydrogen carbonate solution and water, dried, and evaporated. The organic residue was purified by column chromatography (silica; 1 : 3 ethyl acetate–benzene). The first product was the non-conjugated *isothiazolone* (10; R = O·CH_2·CCl_3) (1·5 g.) which crystallised as needles from ethyl acetate, m.p. 171—172°, $[\alpha]_D$ −14·4° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ 3360, 1750, 1670, 1645, 1530, 1240, and 1190 cm.$^{-1}$, $\lambda_{max.}$ 296 nm (log ε 4·03), τ 1·45 (1H, s, 5-H), 2·10br (1H, NH), 2·73 (5H, m, Ph), 4·32 (1H, s, CH·CO_2), 4·78br (2H, s, CH_2=C), 5·10, and 5·42 (2H, ABq, *J* 11 Hz, O·CH_2·CCl_3), 6·33 (2H, s, PhC*H*$_2$), and 8·18 (3H, s, Me) (Found: C, 46·6; H, 3·9; Cl, 22·7; N, 5·5; S, 6·9. $C_{18}H_{17}Cl_3N_2O_4S$ requires C, 46·6; H, 3·7; Cl, 22·8; N, 6·0; S, 6·9%).

Subsequent fractions contained a mixture of the two acetoxy-compounds (2·8 g.). A sample (1·0 g.) was further separated by preparative t.l.c. (1 : 9 acetone–benzene; ×4). From the broad band obtained the leading and tailing quarters were collected. The less polar portion contained ββ*β-trichloroethyl* 2β-*acetoxymethyl*-2α-*methyl*-6β-*phenylacetamidopenam*-3α-*carboxylate* (14; R = O·CH_2·CCl_3) (140 mg.), m.p. (from dichloromethane–ether) 118—119°, $[\alpha]_D^{22}$ +192° (*c* 0·93 in $CHCl_3$), $\nu_{max.}$ 3300, 1780, 1745, 1660, 1550, and 1230 cm.$^{-1}$, τ 2·72 (5H, m, Ph), 3·20br (1H, s, NH), 4·32 (1H, dd, *J* 4 and 11 Hz, 6-H), 4·41 (1H, d, *J* 4 Hz, 5-H), 5·22 (2H, s, O·CH_2·CCl_3), 5·25 (1H, s, 3-H), 5·67, and 6·32 (2H, ABq, *J* 12 Hz, C*H*$_2$·OAc), 6·38 (2H, s, PhC*H*$_2$), 7·98 (3H, s), and 8·48 (3H, s) (Found: C, 45·9; H, 4·2; Cl, 20·6; N, 5·3; S, 6·15. $C_{20}H_{21}Cl_3N_2O_6S$ requires C, 45·9; H, 4·0; Cl, 20·3; N, 5·35; S, 6·1%).

The more polar material was ββ*β-trichloroethyl* 3β-*acetoxy*-3α-*methyl*-7β-*phenylacetamidocepham*-3α-*carboxylate* (13; R = O·CH_2·CCl_3) (20 mg.), isolated as a non-crystalline foam contaminated (^{1}H n.m.r.) by traces of the penam isomer, $[\alpha]_D^{22}$ +35° (*c* 0·9 in $CHCl_3$), $\nu_{max.}$ 3400, 1770, 1725, 1670, and 1500 cm.$^{-1}$, τ 2·70 (5H, m, Ph), 3·92 (1H, d, *J* 9 Hz, NH), 4·40 (1H, dd, *J* 4 and 9 Hz, 6-H), 4·70 (1H, d, *J* 4 Hz, 5-H), 5·18 (1H, s, 4-H), 5·20 (2H, s, O·CH_2·CCl_3), 6·50 and 6·72 (2H, ABq, *J* 14 Hz, CH_2·S), 6·35 (2H, s, PhC*H*$_2$), 8·22 (3H, s), and 8·39 (3H, s). The middle zone on the plate contained 600 mg. of the two products.

When the rearrangement was carried out in acetic anhydride containing anhydrous sodium acetate (0·3 g. in 25 ml.) an isomeric isothiazolone was preferentially formed. This was shown to be the conjugated isomer (11; R = O·CH_2·CCl_3).

Isomerisation of the βγ-Unsaturated Isothiazolone (10; R = O·CH_2·CCl_3).—The ester (100 mg.) in ethyl acetate (15 ml.) was treated with triethylamine (0·1 ml.) at room temperature for 1 hr. The resulting solution was washed with phosphoric acid (20 ml.; 20% v/v) and water, dried, and evaporated *in vacuo*, to give βββ-*trichloroethyl* 3-*methyl*-2-(3-*oxo*-4-*phenylacetamido*-Δ^4-*isothiazolin*-2-*yl*)*but*-2-*enoate* (11; R = O·CH_2·CCl_3), m.p. (from ethyl acetate) 205—207°, $[\alpha]_D^{22}$ 0° (*c* 0·9 in $CHCl_3$), $\nu_{max.}$ 3300, 1715, 1650, 1590, and 1530 cm.$^{-1}$, $\lambda_{max.}$ 295 nm (ε 12,600), τ 1·40 (1H, 5-H), 1·58br (1H, s, NH), 2·69 (5H, m, Ph), 5·36 (2H, s, O·CH_2·CCl_3), 6·28 (2H, s, C*H*$_2$Ph), 7·66 (3H, s), and 8·10 (3H, s) (Found: C, 46·5; H, 3·7; Cl, 22·9; N, 6·1; S, 7·0. $C_{18}H_{17}Cl_3N_2O_4S$ requires C, 46·6; H, 3·7; Cl, 22·8; N, 6·0; S, 6·9%).

Rearrangement of the p-*Nitrobenzyl Ester* (2; R^1 = $PhCH_2$, R^2 = *p*-O_2N·C_6H_4·CH_2·O).—The 6β-phenylacetamidopenicillanate (*S*)-sulphoxide (2 g.) in acetic anhydride (25 ml.) was heated to reflux for 12 min.; the acetic anhydride was then removed *in vacuo*. The residual gum (*ca.* 2·2 g.) was separated by column chromatography (silica gel; 5 : 1 benzene–ethyl acetate) to give three fractions, described in order of elution.

The first fraction crystallised from ethyl acetate to give *p*-nitrobenzyl 3-methyl-2-(3-oxo-4-phenylacetamido-Δ^4-isothiazolin-2-yl)but-3-enoate (10; R = *p*-O_2N·C_6H_4·CH_2·O) (0·45 g., 23%), m.p. 87—95°, $[\alpha]_D^{22}$ −25°, $\lambda_{max.}$ 266 nm (ε 13,300), $\nu_{max.}$ 3290, 1752, 1640, and 1530 cm.$^{-1}$, τ 1·42 (1H, s, 5-H), 2·70 (5H, m, Ph), 4·40br (1H, s, CH·CO_2R), 4·80 (2H, s, CO_2·CH_2), 4·80 and 5·00 (2H, m, CH_2=C), 6·29 (2H, s, PhC*H*$_2$), and 8·19br (3H, s), together with signals for 4 aromatic protons (*p*-nitrobenzyl group).

The second fraction was p-*nitrobenzyl* 7β-*phenylacetamido*-3-*methylceph*-3-*em*-4-*carboxylate* (15; R = *p*-O_2N·C_6H_4·CH_2) (100 mg., 5%), m.p. (from ethyl acetate) 228—234° (decomp.), $[\alpha]_D^{20}$ +63° (*c* 1 in $CHCl_3$), $\lambda_{max.}$ 265 nm (ε 17,300), $\nu_{max.}$ ($CHBr_3$) 3410, 1780, 1728, 1681, and 1526 cm.$^{-1}$, τ 2·70 (5H, m, Ph), 4·25 (1H, dd, *J* 4 and 9 Hz, 7-H), 5·02 (1H, d, *J* 4 Hz, 6-H), 6·39 (2H, s, $PhCH_2$), 6·43 and 6·82 (2H, ABq, *J* 14 Hz, CH_2·S), and 7·85 (3H, s), together with signals from the *p*-nitrobenzyl group (Found: C, 59·4; H, 4·6; N, 8·9; S, 6·9. $C_{23}H_{21}N_3O_6S$ requires C, 59·1; H, 4·5; N, 9·0; S, 6·9%).

The last fraction from the column consisted mainly of p-*nitrobenzyl* 2β-*acetoxymethyl*-2α-*methyl*-6β-*phenylacetamidopenam*-3α-*carboxylate* (14; R = *p*-O_2N·C_6H_4·CH_2·O). A solution of this fraction in ethyl acetate slowly deposited some crystalline material (shown to be the unconjugated isothiazolone by ^{1}H n.m.r. spectroscopy). The residual solution after evaporation *in vacuo* gave, as a gummy solid, the penam (14; R = *p*-O_2N·C_6H_4·CH_2·O) (150 mg., 9%), $[\alpha]_D^{20}$ +51°, $\nu_{max.}$ ($CHBr_3$) 3360, 1685, 1745, 1680, and 1500 cm.$^{-1}$, τ 1·71 and 2·41 (4H, m, *p*-O_2N·C_6H_4), 2·62 (5H, m, Ph), 3·20 (1H, d, *J* 9 Hz, NH), 4·20 (1H, dd, *J* 4 and 9 Hz, 6-H), 4·39 (1H, d, *J* 4 Hz, 5-H), 4·67 (2H, s, CO_2·CH_2), 5·30 (1H, s, 3-H), 5·63 and 6·36 (2H, ABq, *J* 12 Hz, C*H*$_2$·OAc), 6·33 (2H, s, PhC*H*$_2$), 7·86 (3H, s), and 8·58 (3H, s). This compound was further characterised as its sulphoxide derivatives (see later).

Rearrangement of the p-*Nitrobenzyl Ester* (2; R^1 = $PhCH_2$, R^2 = *p*-O_2N·C_6H_4·CH_2·O) *with Chloroacetic Anhydride*.—The ester (10 g.) in toluene (500 ml.) containing

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chloroacetic anhydride (35 g.) was heated at reflux for 2·5 hr. The solvent was removed *in vacuo* and the residue dissolved in ether (20 ml.) was added dropwise to light petroleum (1 l.) with vigorous stirring. The residual oil was dissolved in ethyl acetate–benzene (1 : 5) and filtered through silica gel, with the same solvent mixture as eluant. The major fraction was evaporated to a small volume before precipitation with light petroleum to give, as an amorphous foam, p-*nitrobenzyl* 3β-*chloroacetoxy*-3α-*methyl*-7β-*phenylacetamidocepham*-4α-*carboxylate* (16) (1·7 g.), m.p. 55—80° (decomp.), $[\alpha]_D^{25}$ +30° (*c* 1 in tetrahydrofuran), $\nu_{max.}$ ($CHBr_3$) 3390, 1768, 1738, 1672, and 1522 cm.$^{-1}$, τ 1·79 and 2·51 (4H, *p*-$O_2N{\cdot}C_6H_4$), 2·70 (5H, m, Ph), 3·80 (1H, d, *J* 9 Hz, NH), 4·71 (2H, s, $O{\cdot}CH_2$), 4·41 (1H, dd, *J* 4·5 and 9 Hz, 7-H), 4·76 (1H, d, *J* 4·5 Hz, 6-H), 5·21 (1H, s, 4-H), 6·62 (2H, s, 3β-CH_2), 6·37 (2H, s, PhCH_2), 6·20 (2H, s, CH_2Cl), and 8·47 (3H, s). This sample was characterised as the derived cephem (15; R = *p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$) (see later).

Elimination of Chloroacetic Acid from the Cepham (16).—A solution of the cepham (16) (300 mg.) in acetone (30 ml.) and 0·1N-ammonium hydroxide (25 ml.) was set aside at 10° for 18 hr. The crystalline material that precipitated was collected and crystallised from ethyl acetate to afford *p*-nitrobenzyl 7β-phenylacetamido-3-methylceph-3-em-4-carboxylate (15; R = *p*-$O_2N{\cdot}C_6H_4{\cdot}CH_2$) (102 mg.), m.p. 228—234° (decomp.), identical with the material already described.

Rearrangement of the t-Butylamide (2; R^1 = $PhCH_2$, R^2 = $NHBu^t$).—The amide (1·0 g.) in dry toluene (300 ml.) and acetic anhydride (10 ml.) was heated at reflux for 7 hr. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (30 ml.). The solution was washed with saturated sodium hydrogen carbonate solution and then water, dried, diluted with ether (50 ml.), and left overnight at room temperature. The crystalline precipitate was collected and recrystallised from ethyl acetate (×4) to afford 3β-*acetoxy*-3α-*methyl*-7β-*phenylacetamido*-4α-*t-butylcarbamoylcepham* (13; R = $NHBu^t$) (200 mg.), m.p. 255—257° (decomp.), $[\alpha]_D^{22}$ +14·6° (*c* 0·6 in $CHCl_3$), $\nu_{max.}$ 3340, 3305, 1768, 1740, 1663, 1560, and 1520 cm.$^{-1}$, τ 2·66 (5H, m, Ph), 3·58 (1H, s, NH), 3·77 (1H, d, *J* 9 Hz, NH), 4·40 (1H, dd, *J* 4 and 9 Hz, 7-H), 4·67 (1H, d, *J* 4 Hz, 6-H), 5·51 (1H, s, 4-H), 6·14 and 6·76 (2H, ABq, *J* 14 Hz, $CH_2{\cdot}S$), 8·22 (3H, s), 8·45 (3H, s), and 8·68 (9H, s, Bu^t) (Found: C, 58·8; H, 6·2; N, 9·0; S, 7·3. $C_{22}H_{29}N_3O_5S$ requires C, 59·65; H, 6·5; N, 9·4; S, 7·2%).

The mother liquors from the foregoing experiment showed n.m.r. bands consistent with the presence of the penam isomer, in lower yield than that of the cepham, but this was not isolated.

When the rearrangement was repeated with the starting amide (3·4 g.) in toluene (150 ml.) containing acetic anhydride (6 ml.) and anhydrous sodium acetate (35 mg.) the first crop of crystals isolated from the work-up procedure were 3-*methyl*-2-(3-*oxo*-4-*phenylacetamido*-Δ^4-*isothiazolin*-2-*yl*)-N-*t-butylbut*-3-*enamide* (10; R = $NHBu^t$) (0·46 g.), m.p. (from ethyl acetate) 200—202°, $[\alpha]_D^{22}$ −13°(*c* 1·0 in $CHCl_3$), $\nu_{max.}$ 3340, 3280, 1700, 1690, 1670, 1632, 1618, 1600, 1540, and 1370 cm.$^{-1}$, $\lambda_{max.}$ 298 nm (log ε 4·04), τ 1·75 (1H, s, 5-H), 2·66 (5H, m, Ph), 3·97 (1H, s, NH), 4·52br (1H, s, N·CH·CO), 4·89br (2H, s, CH_2=C), 6·26 (2H, s, PhCH_2), 8·30 (3H, s), and 8·69 (9H, s) (Found: C, 61·6; H, 6·4; N, 10·8; S, 7·8. $C_{20}H_{25}N_3O_3S$ requires C, 62·0; H, 6·5; N, 10·9; S, 8·3%).

Correlation of the t-Butylamide (13; R = $NHBu^t$) *with the Trichloroethyl Ester* (13; R = $O{\cdot}CH_2{\cdot}CCl_3$).—The trichloroethyl ester (50 mg.) in aqueous acetic acid (1 : 9; 10 ml.) was stirred with zinc dust (100 mg.) for 1 hr. at room temperature. The mixture was filtered and evaporated to dryness *in vacuo* before addition of phosphoric acid (20% v/v) and extraction with dichloromethane. The dried organic extract was treated with triethylamine (0·015 ml.) and ethyl chloroformate (0·010 ml.) at 0° for 30 min. t-Butylamine (0·105 ml.) was added and stirring was continued for 1 hr. at room temperature. Work-up in the usual manner afforded, after preparative t.l.c., the t-butylamide (10 mg.), identical (m.p., mixed m.p., i.r., and n.m.r.) with the sample prepared previously.

(1S)-3β-*Acetoxy*-3α-*methyl*-7β-*phenylacetamido*-4α-*t-butylcarbamoylcepham* 1-*Oxide* (19; R = $NHBu^t$).—The sulphide (330 mg.) in dichloromethane (10 ml.) at room temperature was stirred with 1·1M-monoperphthalic acid in ether (0·74 ml.). After 5 min. the solution was washed with aqueous sodium hydrogen carbonate solution, dried, and evaporated to dryness. The residue was dissolved in ethanol (5 ml.). The *sulphoxide* (19; R = $NHBu^t$) was deposited as prisms (175 mg., 51%), m.p. (from ethanol), *ca.* 100° (loses water of crystallisation and crystallises again) and 218—222°, $[\alpha]_D^{20}$ −32° (*c* 0·2 in tetrahydrofuran), $\nu_{max.}$ ($CHBr_3$) 1768, 1730, 1670, 1510, and 1215 cm.$^{-1}$, τ 2·57 (1H, s, NH), 2·74 (5H, m, Ph), 3·30 (1H, s, NH), 4·00 (1H, dd, *J* 9 and 4·5 Hz, 7-H), 5·03 (1H, d, *J* 4·5 Hz, 6-H), 5·40 (1H, s, 4-H), 5·67 and 6·65 (2H, ABq, *J* 15 Hz, $SO{\cdot}CH_2$), 6·46 (2H, s, PhCH_2), 8·12 (3H, s, Ac), 8·42 (3H, s), and 8·69 (9H, s) (Found: C, 56·2; H, 6·3; N, 8·6; S, 6·4. $C_{22}H_{19}N_3O_6S,0{\cdot}5H_2O$ requires C, 55·9; H, 6·4; N, 8·9; S, 6·8%).

3β-*Acetoxy*-3α-*methyl*-7β-*phenylacetamido*-4α-*t-butylcarbamoylcepham* 1,1-*Dioxide* (20; R = $NHBu^t$).—The sulphide (280 mg.) in dichloromethane (10 ml.) was treated with 1·1M-monoperphthalic acid in ether (1·5 ml.) at room temperature. After 5 min. the solution was washed with aqueous sodium hydrogen carbonate and evaporated to a foam. A solution of the foam in ethanol (5 ml.) deposited white crystals of the *sulphone* (225 mg., 75%), m.p. 210—214°, $[\alpha]_D^{20}$ −14° (*c* 1·0 in tetrahydrofuran), $\nu_{max.}$ ($CHBr_3$) 3410, 3370, 1779, 1736, 1676, 1510, and 1214 cm.$^{-1}$, τ 2·75 (5H, m, Ph), 2·93 (1H, d, *J* 9 Hz, NH), 3·36 (1H, s, NH), 4·01 (1H, dd, *J* 4·5 and 9 Hz, 7-H), 4·86 (1H, d, *J* 4·5 Hz, 6-H), 5·56 (1H, s, 4-H), 5·93 and 6·10 (2H, ABq, *J* 14 Hz, $SO_2{\cdot}CH_2$), 6·41 (2H, s, PhCH_2), 8·10 (3H, s), 8·33 (3H, s), and 8·70 (9H, s) (Found: C, 54·9; H, 6·3; N, 8·6; S, 6·5. $C_{22}H_{29}N_3O_7S$ requires C, 55·1; H, 6·1; N, 8·8; S, 6·7%).

(1R)-3β-*Acetoxy*-3α-*methyl*-7β-*phenylacetamido*-4α-*t-butylcarbamoylcepham* 1-*Oxide* (21; R = $NHBu^t$).—The sulphide (700 mg.) in dioxan (20 ml.) was treated with sodium periodate (2·5 g.) in water (10 ml.) at room temperature for 3 days. The solution was then diluted with water (100 ml.) and extracted with ethyl acetate (3 × 20 ml.). The combined organic layers were washed with water, dried, and evaporated *in vacuo* to give a foam (530 mg.). Preparative t.l.c. (1 : 1 ethyl acetate–benzene) afforded as an amorphous solid, the (R)-*sulphoxide*, m.p. 115—120°, $[\alpha]_D^{22}$ −32·9° (*c* 0·5 in $CHCl_3$), $\nu_{max.}$ 3550, 3360, 1775, 1745, 1675, 1540, 1220, and 1030 cm.$^{-1}$ (Found: C, 57·1; H, 6·15; N, 9·0; S, 6·6. $C_{22}H_{29}N_3O_6S$ requires C, 57·0; H, 6·3; N, 9·1; S, 6·9%).

(1S)-6β(*p-Bromophenyl*)*acetamidopenicillanic Acid* 1-*Oxide*.—Triethylammonium 6β-(*p*-bromophenyl)acetamidopenicillanate (7·3 g.) in water (350 ml.) containing phosphate buffer (pH 6·8) and sodium periodate (3·9 g.) was stirred at room temperature for 3 hr. The mixture was acidified to

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pH 2 with phosphoric acid before extraction with ethyl acetate (400 ml.). The extract was washed with water, dried, and evaporated to dryness to give the acid (4 g.), $\nu_{max.}$ ($CHCl_3$) 3350, 1780, 1720, 1680, 1520, and 1460 $cm.^{-1}$. The acid (2·0 g.) was characterised as its t-butylamide, prepared as described previously. Recrystallisation of the amide from ethyl acetate afforded, as plates, (1S)-6β-(p-*bromophenyl*)*acetamido*-2,2-*dimethyl*-3α-*t-butylcarbamoylpenam* 1-*oxide* (2; R^1 = *p*-$BrC_6H_4CH_2$, R^2 = $NHBu^t$) (1·93 g.), m.p. 183—184°, $[\alpha]_D^{22}$ +196° (*c* 0·8 in $CHCl_3$), $\nu_{max.}$ 3350, 1780, 1685, 1650, 1540, and 1520 $cm.^{-1}$, τ 2·75 (4H, m, *p*-BrC_6H_4), 3·7br (2H, NH), 4·00 (1H, dd, *J* 5 and 10 Hz, 6-H), 5·10 (1H, d, *J* 5 Hz, 5-H), 5·62 (1H, s, 3-H), 6·45 (2H, s, $ArCH_2$), 8·25 (3H, s), 8·62 (9H, s), and 8·78 (3H, s) (Found: C, 49·8; H, 5·4; Br, 16·4; N, 8·6. $C_{20}H_{26}BrN_3O_4S$ requires C, 49·9; H, 5·4; Br, 16·6; N, 8·4%).

(1R)-3β-*Acetoxy*-7β-(p-*bromophenyl*)*acetamido*-3α-*methyl*-4α-*t-butylcarbamoylcepham* 1-*oxide* (18).—The penam t-butyl-amide (1·2 g.) was heated in refluxing toluene (300 ml.) containing acetic anhydride (10 ml.) for 7 hr. The solvent was removed under reduced pressure and a solution of the residue in ethyl acetate (30 ml.) was washed with sodium hydrogen carbonate solution, dried, and evaporated to dryness. The residue, in ether, deposited crystals of the t-butyl-amide (18; as sulphide) (300 mg.), the majority of which was directly oxidised with sodium periodate. A portion of the sulphide had $[\alpha]_D^{22}$ +34° (*c* 0·4 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400, 1770, 1730, 1680, and 1510 $cm.^{-1}$, τ 2·75 (4H, *p*-BrC_6H_4), 3·65br (2H, NH), 4·35 (1H, dd, *J* 4 and 9 Hz, 7-H), 4·70 (1H, d, *J* 4 Hz, 6-H), 5·50 (1H, s, 4-H), 6·21 and 6·82 (2H, AB, *J* 15 Hz, CH_2·S), 6·42 (2H, s, $ArCH_2$), 8·20 (3H, s), 8·45 (3H, s), and 8·63 (9H, s).

Oxidation of the sulphide (250 mg.) with sodium periodate (1·5 g.) in buffered aqueous dioxan, as already described, afforded (7 days at room temperature; isolation by preparative t.l.c.) the title (R)-*sulphoxide* (130 mg.), m.p. (from dichloromethane) 227—228°, $[\alpha]_D^{22}$ −45° (*c* 0·1 in $CHCl_3$), $\nu_{max.}$ 3320, 1775, 1740, 1670, 1550, and 1215 $cm.^{-1}$, τ 2·65 (4H, m, *p*-O_2N·C_6H_4), 3·7 (1H, d, *J* 9 Hz, NH), 4·70 (1H, dd, *J* 4 and 9 Hz, 7-H), 5·0 (1H, d, *J* 4 Hz, 6-H), 5·3 (1H, s, 4-H), 6·2 (2H, s, CH_2·S), 6·42 (2H, s, $ArCH_2$), 8·01 (3H, s), 8·34 (3H, s), and 8·63 (9H, s), M^+ 541·543. (Found: C, 48·8; H, 5·2; N, 7·75. $C_{22}H_{28}BrN_3O_6S$ requires C, 48·7; H, 5·2; N, 7·8%).

Trichloroethyl (1R)-2β-*Acetoxymethyl*-2α-*methyl*-6β-*phenylacetamidopenam*-3α-*carboxylate* 1-*Oxide* (22; R = O·CH_2·CCl_3).—The sulphide (14; R = O·CH_2·CCl_3) (2·0 g.) in aqueous pyridine (5 ml. water in 60 ml.) at −35° was treated with iodobenzene dichloride (2·5 g.) with stirring for 30 min. The mixture was then poured into 20% v/v phosphoric acid (250 ml.) and extracted with ethyl acetate (3 × 25 ml.). The extract was washed with water, dried, and evaporated to dryness. The residue was chromatographed through silica gel (1 : 2 ethyl acetate–benzene) to give, initially, *trichloroethyl* (1S)-2β-*acetoxymethyl*-2α-*methyl*-6β-*phenylacetamidopenam*-3α-*carboxylate* 1-*oxide* (24; R = O·CH_2·CCl_3) (0·60 g.), as an amorphous solid, $[\alpha]_D^{22}$ +184° (*c* 0·9, $CHCl_3$), $\nu_{max.}$ ($CHBr_3$) 3300, 1775, 1760, 1725, 1670, 1540, and 1230 $cm.^{-1}$, τ 2·65 (5H, m, Ph), 2·92 (1H, d, *J* 9 Hz. NH), 3·99 (1H, dd, *J* 4 and 9 Hz, 6-H), 5·05 (1H, d, *J* 4 Hz, 5-H), 5·18 (1H, s, 3-H), 5·30 (2H, s, O·CH_2·CCl_3), 5·26 and 5·52 (2H, ABq, *J* 12 Hz, CH_2·OAc), 6·48 (2H, s, $PhCH_2$), 7·94 (3H, s), and 8·73 (3H, s) (Found: C, 44·7; H, 4·0; N, 5·2; S, 5·7. $C_{20}H_{21}Cl_3N_2O_7S$ requires C, 44·5; H, 3·9; N, 5·2; S, 5·9%). This sulphoxide could also be prepared by oxidation of the acetoxymethyl sulphide with either sodium periodate or *m*-chloroperbenzoic acid.

Further elution of the column, with 1 : 1 benzene–ethyl acetate, afforded *trichloroethyl* (1R)-2β-*acetoxymethyl*-2α-*methyl*-6β-*phenylacetamidopenam*-3α-*carboxylate* 1-*oxide*. (22); R = O·CH_2·CCl_3) (0·7 g.), $[\alpha]_D^{22}$ +137° (*c* 0·9 in $CHCl_3$) $\nu_{max.}$ ($CHBr_3$) 3300, 1780, 1745, 1670, and 1520 $cm.^{-1}$, τ 2·73 (5H, m, phenyl), 3·20br (1H), 4·82 (1H, dd, *J* 4 and 11 Hz, 6-H), 5·21 (1H, d, *J* 4 Hz, 5-H), 5·25 (1H, s, 3-H), 5·22 (2H, s, CH_2·CCl_3), 5·40 (2H, s, CH_2·OAc), 6·42 (2H, s, $PhCH_2$), 8·00 (1H, s, Ac), and 8·62 (3H. s) (Found: C, 45·0; H, 4·1; N, 5·2. $C_{20}H_{21}Cl_3N_2O_7S$ requires C, 44·5; H, 3·9; N, 5·2%).

Trichloroethyl (1S)-2α-*Acetoxymethyl*-2β-*methyl*-6β-*phenylacetamidopenam*-3α-*carboxylate* 1-*Oxide* (23; R = O·CH_2·CCl_3) —The (*R*)-sulphoxide (22; R = O·CH_2·CCl_3) (100 mg) in dry toluene (200 ml.) was heated at reflux for 30 min. Solvent was removed *in vacuo* and the residue was purified by preparative t.l.c [ethyl acetate–benzene (1 : 1)] to give the isomeric (S)-*sulphoxide* (80 mg.) as a non-crystalline foam, $[\alpha]_D^{22}$ +181° (*c* 1·0 in $CHCl_3$), $\nu_{max.}$ ($CHBr_3$) 3300, 1770, 1745, 1670, 1540, and 1230 $cm.^{-1}$, τ 2·70br (5H, s, Ph), 3·94 (1H, dd, *J* 4 and 9 Hz, 6-H), 4·98 (1H, d, *J* 4 Hz, 5-H), 5·20 (1H, s, 3-H), 5·16 and 5·35 (2H, AB, *J* 12 Hz, O·CH_2·CCl_3), 5·43 and 6·02 (2H, ABq, *J* 12·5 Hz, CH_2·OAc), 6·44 (2H, s, $PhCH_2$), 7·98 (3H, s, Ac), and 8·30 (3H, s) (Found: C, 44·7; H, 4·1; Cl, 19·9; N, 5·2; S, 6·1. $C_{20}H_{21}Cl_3N_2O_7S$ requires C, 44·5; H, 3·9; Cl, 19·8; N, 5·2 S, 6·0%).

p-*Nitrobenzyl* (1R)-2β-*Acetoxymethyl*-2α-*methyl*-6β-*phenylacetamidopenam*-3α-*carboxylate* 1-*Oxide* (22; R = *p*-O_2N·C_6H_4·CH_2·O).—The sulphide (14; R = *p*-O_2N·C_6H_4·CH_2·O) (4·0 g.) in pyridine (100 ml.) and water (5 ml.) at −45° was treated with t-butyl hypochlorite (1·4 ml.) for 2 min. 2N-Sulphurous acid (2 ml.) was added and the mixture was poured into phosphoric acid (1 : 4 orthophosphoric acid–water) (500 ml.) and ethyl acetate (100 ml.). The aqueous layer was re-extracted with ethyl acetate (2 × 100 ml.) and the combined organic layers were washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated. The products (4·05 g.) were separated by chromatography through silica gel (40 g.) [benzene–ethyl acetate (2 : 1, 500 ml.; 1 : 1, 1 l.) as eluant] to afford, initially, p-*nitrobenzyl* (1S)-2β-*acetoxymethyl*-2α-*methyl*-6β-*phenylacetamidopenam*-3α-*carboxylate* 1-*oxide* (24; R = *p*-O_2N·C_6H_4·CH_2·O) (0·76 g.), isolated as an amorphous powder, $[\alpha]_D^{22}$ +120° (*c* 1·0 in tetrahydrofuran), $\lambda_{max.}$ 261 nm (ε 10,600), $\nu_{max.}$ ($CHBr_3$) 1800, 1750, 1682, and 1528 $cm.^{-1}$, τ 1·80 and 2·49 (4H, m, *p*-O_2N·C_6H_4), 2·74 (5H, m, Ph), 2·96 (1H, d, *J* 9 Hz, NH), 3·98 (1H, dd, *J* 9 and 4·5 Hz, 6-H), 4·72 (2H, s, CO_2·CH_2), 5·06 (1H, d, *J* 4·5 Hz, 5-H), 5·37 (1H, s, 3-H), 5·30 and 5·60 (2H, ABq, *J* 12 Hz, CH_2·OAc), 6·44 (2H, s, $PhCH_2$), 7·91 (3H, s, Ac), and 8·90 (3H, s) (Found: C, 55·6; H, 4·6; N, 7·5; S, 5·6. $C_{25}H_{25}N_3O_9S$ requires C, 55·3; H, 4·6; N, 7·7; S, 5·9%).

The second component eluted was the title (R)-*sulphoxide* (1·94 g.), isolated as an amorphous foam, $[\alpha]_D^{22}$ +95° (*c* 1 in tetrahydrofuran). $\lambda_{max.}$ 263 nm (ε 10.800), $\nu_{max.}$ ($CHBr_3$) 3410, 1798, 1748, 1682, and 1510 $cm.^{-1}$, τ 1·80 and 2·47 (4H, m, *p*-O_2N·C_6H_4), 2·72 (5H, m, Ph), 3·34 (1H, d, *J* 9 Hz, NH), 4·72 (2H, s, CO_2·CH_2), 5·31 (1H, s, 3-H), 5·61 (2H, s, CH_2·OAc), 6·40 (2H, s, $PhCH_2$), 8·00 (3H, s, Ac), and 8·78 (3H, s) (Found: C, 55·3; H, 4·6; N, 7·8; S, 5·7. $C_{25}H_{25}N_3O_9S$ requires C, 55·3; H, 4·6; N, 7·7; S, 5·9%).

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p-*Nitrobenzyl* (1S)-2α-*Acetoxymethyl*-2β-*methyl*-6β-*phenylacetamidopenam*-3α-*carboxylate* 1-*Oxide* (23; R = *p*-O_2N·C_6H_4·CH_2·O).—The 2β-acetoxymethyl-(*R*)-sulphoxide (22; R = *p*-O_2N·C_6H_4·CH_2·O) (1·0 g.) was heated in refluxing toluene (300 ml.) for 15 min. The solvent was evaporated off under reduced pressure and the residue was chromatographed on silica gel (40 g.) (4 : 1 benzene–ethyl acetate). This afforded a foam (0·67 g.), which crystallised from ethyl acetate as the (S)-*sulphoxide*, m.p. 133—134°, $[\alpha]_D^{22}$ +118° (*c* 1 in tetrahydrofuran), $\lambda_{max.}$ 262 nm (ε 10,600), $\nu_{max.}$ 3380, 1790, 1744, 1673, and 1520 cm.$^{-1}$, τ 1·80 and 2·50 (4H, m, *p*-O_2N·C_6H_4), 2·78 (5H, m, Ph), 3·00br (1H, s, NH), 3·97 (1H, dd, *J* 9 and 4·5 Hz, 6-H), 4·92 (1H, d, *J* 4·5 Hz, 5-H), 4·78 (2H, s, CO_2·CH_2), 5·32 (1H, s, 3-H), 5·56 and 6·13 (2H, ABq, *J* 13 Hz, CH_2·OAc), 6·47 (2H, s, PhCH_2), 8·02 (3H, s, Ac), and 8·38 (3H, s) (Found: C, 55·4; H, 4·6; N, 7·4; S, 5·7. $C_{25}H_{25}N_3O_9S$ requires C, 55·3; H, 4·6; N, 7·7; S, 5·9%).

Sodium 2α-*Acetoxymethyl*-2β-*methyl*-6β-*phenylacetamidopenam*-3α-*carboxylate* (26; R = ONa).—The sulphoxide (23; R = *p*-O_2N·C_6H_4·CH_2·O) (0·8 g.) was treated at 0° with phosphorus tribromide (0·7 ml.) in dimethylformamide (25 ml.) for 10 min. The solution was then poured into aqueous sodium hydrogen carbonate solution (100 ml.) and extracted with ethyl acetate (3 × 50 ml.). The extracts were washed with water (3 × 50 ml.), dried ($MgSO_4$), and evaporated to give *p*-nitrobenzyl 2α-acetoxymethyl-2β-methyl-6β-phenylacetamidopenam 3α-carboxylate (26; R = *p*-O_2N·C_6H_4·CH_2·O) (0·8 g.) as a yellow foam, $\lambda_{max.}$ 264 nm (ε 10,300), $\nu_{max.}$ ($CHBr_3$), 1790, 1748, 1648, and 1520 cm.$^{-1}$, τ 1·80 and 2·52 (4H, m, *p*-O_2N·C_6H_4), 2·72 (5H, m, Ph), 3·89 (1H, d, *J* 9 Hz, NH), 4·37 (1H, dd, *J* 4·5 and 9 Hz, 6-H), 4·52 (1H, d, *J* 4·5 Hz, 5-H), 4·80 (2H, s, CO_2·CH_2), 5·52 (1H, s, 3-H), 5·88 and 5·94 (2H, ABq, *J* 13 Hz CH_2·OAc), 6·39 (2H, s, PhCH_2), 8·02 (3H, s, Ac), and 8·51 (3H, s). This product (0·8 g.) was shaken with activated charcoal (1·5 g.) in dry tetrahydrofuran (75 ml.) for 5 min. at room temperature. The mixture was then filtered and hydrogenated over 10% palladium–charcoal (1·5 g.) at room temperature and pressure (uptake 100 ml.). The catalyst was filtered off and the filtrate was treated with water (100 ml.), diethyl ether (50 ml.), and light petroleum (50 ml.). The mixture was stirred vigorously while the pH was adjusted to 7·0 with sodium hydrogen carbonate solution. The aqueous layer was separated and the organic layer was again treated with water (100 ml.) and adjusted to pH 7. The combined aqueous layers were washed with ethyl acetate (3 × 50 ml.) and freeze-dried. The resulting solid was dissolved in acetone (10 ml.) and, after removal of some insoluble material, the solution was poured into ether (100 ml.) to precipitate the *sodium salt* (0·37 g.), $[\alpha]_D^{23}$ +218° (*c* 1 in H_2O), $\nu_{max.}$ 1770, 1735, 1655, 1615, and 1535 cm.$^{-1}$, τ (D_2O) 2·64 (5H, m, Ph), 4·48 (1H, d, *J* 4 Hz, 6-H), 4·54 (1H, d, *J* 4 Hz, 5-H), 5·66 (1H, s, 3-H), 5·67 and 5·82 (2H, ABq, *J* 12 Hz, CH_2·OAc), 6·33 (2H, s, PhCH_2), 7·88 (3H, s, Ac), and 8·38 (3H, s) (Found: C, 46·0; H, 5·2; N, 5·7; S, 6·5. $C_{18}H_{19}N_2NaSO_6,3H_2O$ requires C, 46·2; H, 5·4; N, 6·0; S, 6·8%).

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