Transformations of Penicillin. Part III.† A New Route to 2,2-Dimethyl-6β-phenylacetamidopenam-3α-ol *S*-Oxide and its Esters; *o*-Nitrobenzoate as a Protecting Group for Alcohols and Phenols

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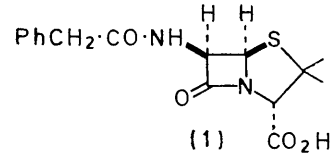
Esters of the title compound have been obtained by rearrangement of aroyl penicillanoyl peroxides, followed by decarboxylation. Certain of the aroyl esters so produced have been epimerised at position 6 with selected secondary amines. Conditions for the liberation of the title alcohol from some of its aroyl esters have been established. Thus, the 2,4-dinitrobenzoate can either be photohydrolysed, by irradiation in aqueous tetrahydrofuran, or reduced with sodium borohydride. *o*-Nitrobenzoate is a potentially useful protecting group for alcohols and phenols since the group can be removed in high yield by reduction with zinc dust and ammonium chloride; the alcohol is liberated with formation of 2,1-benzisoxazolin-3-one. In this manner the title alcohol was obtained from its *o*-nitrobenzoate in 95% yield.

ONE route for the selective cleavage of the thiazolidine ring in penicillins involves Curtius degradation of the 3-carboxylic acid (1).[1a] The resulting 3-hydroxypenam (2) is in equilibrium with the ring-opened aldehyde (3), the position of equilibrium depending on the nature of the penam substituents, but generally lying in favour of the carbinolamine [*e.g.* (2)].[1b] The alcohol sulphoxide (4) has been employed in trapping reactions of the derived sulphenic acid.[2] However, since large-scale reactions involving the Curtius rearrangement (*viz.* thermal treatment of the acyl azides) are potentially hazardous and yields variable,[3] an alternative route to the alcohol (4) was developed.



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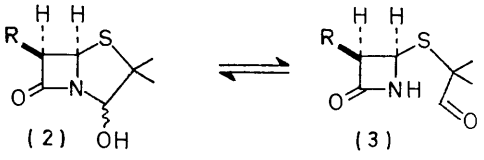

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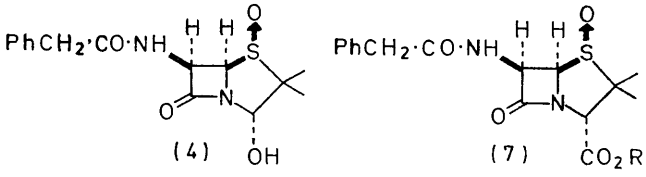


(4) (7)

The method employed involves the decarboxylative rearrangement of alkanoyl aroyl peroxides [4] (see Scheme).

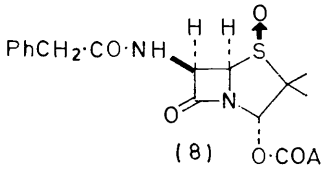
$$RCO{\cdot}O{\cdot}O{\cdot}COAr \longrightarrow RO{\cdot}CO{\cdot}O{\cdot}COAr \longrightarrow RO{\cdot}COAr + CO_2$$

(5) (6)

SCHEME

Such peroxides (5) rearrange into the 'inversion' product (6) with retention of configuration at the alkyl centre.[5] On warming, the 'inversion' intermediates decarboxylate to produce the corresponding esters.

(*S*)-6β-Phenylacetamidopenicillanic acid *S*-oxide [6] (7; R = H) was converted into its mixed anhydride with



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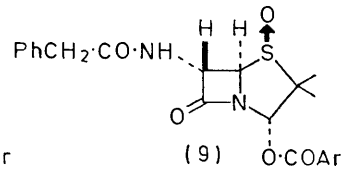

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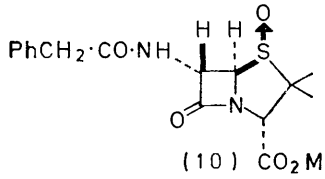


(10)

ethyl chloroformate in the presence of triethylamine; the anhydride, in anhydrous chloroform, was then treated with *m*-chloroperbenzoic acid at low temperature. On warming the reaction mixture to ambient temperature overnight, decarboxylation occurred and, in this way, a high yield of the corresponding ester (8; Ar = *m*-ClC_6H_4) was obtained. Coupling of the penicillanic acid (7; R = H) with the aromatic peroxides could also be achieved by use of *NN'*-dicyclohexylcarbodi-imide instead of ethyl chloroformate.[7] When the reaction mixture was not kept strictly anhydrous small quantities of the required 3-hydroxypenam (4) and the ethyl ester (7; R = Et) were also formed. Attempts to increase the production of the alcohol (4) by addition of more water, or of methanol or even acetic acid to the reaction mixture proved detrimental; lower overall yields of the ester (8; Ar = *m*-ClC_6H_4) and alcohol (4) were obtained.

The small quantity of alcohol formed in the foregoing reaction may arise *via* hydrolysis of the labile mixed anhydride intermediate (5). That the alcohol (4) had the 3α-configuration was determined by its conversion

† Part II, D. H. R. Barton, M. Girijavallabhan, and P. G. Sammes, *J.C.S. Perkin I*, 1972, 929.

[1] (*a*) J. C. Sheehan and K. G. Brandt, *J. Amer. Chem. Soc.*, 1965, **87**, 5468; (*b*) K. Heusler, *Helv. Chim. Acta*, 1972, **55**, 388.

[2] D. H. R. Barton, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, B. E. Looker, and W. G. E. Underwood, *Chem. Comm.*, 1971, 1137.

[3] P. S. A. Smith, *Org. Reactions*, 1946, **3**, 337.

[4] P. B. Denney and N. Sherman, *J. Org. Chem.*, 1965, **30**, 3760.

[5] F. D. Greene, H. P. Stein, C.-C. Chu, and F. M. Vane, *J. Amer. Chem. Soc.*, 1964, **86**, 2081.

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

[7] F. D. Greene and J. Kazan, *J. Org. Chem.*, 1963, **28**, 2168.

into the *m*-chlorobenzoate (8; Ar = *m*-ClC_6H_4) with *m*-chlorobenzoyl chloride. No sign of any epimers of the alcohol (4) was observed in its ^1H n.m.r. spectrum. Furthermore, none of the aldehyde corresponding to the ring-opened isomer [*cf.* (2) ⇌ (3)] was present, although this is not surprising since the presence of the strong intramolecular sulphoxide–amide hydrogen bond would tend to inhibit rotation about the C(5)–S bond, hence restricting opening of the carbinolamine.

Attempted hydrolysis of the ester (8; Ar = *m*-ClC_6H_4) by aqueous acid or base proved abortive. In an attempt to effect selective aminolysis of the ester function, without cleavage of the β-lactam ring, the ester (8; Ar = *m*-ClC_6H_4) was treated with diethylamine in anhydrous tetrahydrofuran. A clean reaction ensued at room temperature but the product was not the required alcohol (4). Instead, the epimeric ester (9; Ar = *m*-ClC_6H_4) was formed. That epimerization had occurred about position 6 was reflected by the ^1H n.m.r. spectrum, the β-lactam protons resonating at τ 4·72 (1H, d, *J* 2 Hz) and 5·08 (1H, dd, *J* 2 and 8 Hz). Solvent shift studies * confirmed the centre of epimerization as position 6. Treatment of the epimer (9; Ar = *m*-ClC_6H_4) with diethylamine re-established the 6α : 6β equilibrium (ratio 1 : 1), although the reverse process was faster.† In view of the observed epimerization other bases were tried. The ester (8; Ar = *m*-ClC_6H_4) was also epimerized about position 6 by 2,2,6,6-tetramethylpiperidine, triethylamine, and di-isopropylethylamine but the rates were very low compared with that for diethylamine.

Epimerization about position 6 has considerable precedent for both penicillin and cephalosporin derivatives. However, although unprotected cephalosporin *S*-oxides have been epimerized about position 7 with base,[8] previous reports of the epimerization for penicillins has always involved derivatives with the 6β-amide function protected, for example, either by silylation,[9] or by using the 6β-phthalimido-derivative.[10] Normally, the sensitivity to base of penicillins having the 6β-amide function unprotected has precluded a study of epimerization about position 6. It is probable that diethylamine is especially effective because, first, its relative bulk inhibits direct attack at the β-lactam function and, secondly, it can compete successfully with the 6β-amide group for hydrogen bonding to the sulphoxide. Intramolecular sulphoxide–6α-amide hydrogen bonding is unlikely. The generality of diethylamine as an epimerization catalyst was confirmed by applying it to the methyl ester (7; R = Me). Again a smooth epimerization occurred, to give the 6α-epimer (10).

The presence of the intramolecular hydrogen bond between the sulphoxide and side-chain amide groups is demonstrated by the equilibrium ratio of 6α- and 6β-epimers, which, for the ester (8; Ar = *m*-ClC_6H_4) approached 1 : 1. In the absence of the sulphoxide group epimerization about position 6 generally favours the 6α-isomer in order to release steric interactions across the *cis*-fused penam skeleton.[11] The presence of the hydrogen bond in the 6β-substituted sulphoxide (8; Ar = *m*-ClC_6H_4) counteracts such steric strain and the equilibrium distributes almost equally between the two epimers. This effect could be useful for transforming 6α-penams into the biologically active 6β-series. At present the only useful, alternative method of converting 6α-amino-substituents into the 6β-isomers is *via* their arylmethylene derivatives.[12]

Decarboxylation of the sulphoxide acid (7; R = H) was also effected with *o*-nitro-[13] and *p*-nitro-perbenzoic[14] acids to give the esters (8; Ar = *o*-$NO_2{\cdot}C_6H_4$) and (8; Ar = *p*-$NO_2{\cdot}C_6H_4$), respectively, both in high yield. Again the products were identical with those produced directly by acylation of the 3-hydroxypenam (4). The *p*-nitrobenzoate (8; Ar = *p*-$NO_2{\cdot}C_6H_4$) could also be epimerized with diethylamine. Attempted aminolysis of the *o*-nitrobenzoate with imidazole likewise caused isomerization into compound (9; Ar = *o*-$NO_2{\cdot}C_6H_4$). Neither the *o*-nitro- (8; Ar = *o*-$NO_2{\cdot}C_6H_4$) nor the *p*-nitro-benzoate (8; Ar = *p*-$NO_2{\cdot}C_6H_4$) could be hydrolysed by conventional means. However, photolysis of the *o*-nitrobenzoate in aqueous tetrahydrofuran did give traces of the 3-hydroxypenam (4). For this reason the 2,4-dinitrobenzoate [8; Ar = 2,4-$(NO_2)_2C_6H_3$] was also made and subjected to photolysis. In this case a much higher yield of the required alcohol (4) was obtained (20%) but this could not be increased by varying the reaction conditions.

Another approach adopted was reductive cleavage of the aromatic ester function. Since sodium borohydride is known to reduce activated esters[15] it was used on the aromatic ester of the 3-hydroxypenam (4). The dinitrobenzoate [8; Ar = 2,4-$(NO_2)_2C_6H_4$] reacted smoothly with sodium borohydride in methanol at 0° to give the alcohol (11) in moderate yield but the other benzoates described were only attacked by the reagent slowly and, although some of the carbinol (11) was formed, in most of the products the β-lactam group was missing.

One further type of reduction, employing a reaction

* For solvent shift arguments see ref. 10 (*c*).

† As noted by a referee, for a true equilibrium ratio of 1 : 1 the rates of the forward and reverse processes in the equilibration reaction should be the same. In the present work the accurate rates have *not* been determined. Furthermore, prolonged reaction times lead to eventual destruction of the equilibrated products and these side reactions can effect the apparent rates of establishment of equilibrium.

[8] M. L. Sassiver and R. G. Shepherd, *Tetrahedron Letters*, 1969, 3993.

[9] G. E. Gutowski, *Tetrahedron Letters*, 1970, 1779; A. Vlietnik, E. Roets, P. Claes, and H. Vanderhaeghe, *ibid.*, 1972, 285.

[10] (*a*) S. Wolfe and W. S. Lee, *Chem. Comm.*, 1969, 242; (*b*) B. G. Ramsey and R. J. Stoodley, *ibid.*, 1971, 450; (*c*) R. D. G. Cooper, P. V. de Marco, and D. O. Spry, *J. Amer. Chem. Soc.*, 1969, **91**, 1528.

[11] J. P. Clayton, J. H. C. Nayler, R. Southgate, and E. R. Stove, *Chem. Comm.*, 1969, 129.

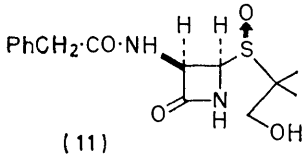
[12] J. R. Jackson and R. J. Stoodley, *Chem. Comm.*, 1970, 1577; *J.C.S. Perkin I*, 1972, 895.

[13] L. S. Silbert, E. Siegel, and D. Swern, *J. Org. Chem.*, 1962, **27**, 1336.

[14] M. Vilkas, *Bull. Soc. chim. France*, 1959, 1401.

[15] S. Takahashi and L. A. Cohen, *J. Org. Chem.*, 1970, **35**, 1505.

originally described by Bamberger in 1909,[16] involved the action of zinc and ammonium chloride on the *o*-nitrobenzoate (8; Ar = *o*-NO_2·C_6H_4). The initial reduction product was the *o*-hydroxyaminobenzoate, which immediately reacted by intramolecular displacement of the alcohol (4) with liberation of 2,1-benzisoxazolin-3-one (12). Because of the high yield of alcohol (>95%) in this reaction the general applicability of the *o*-nitrobenzoate function as a protecting group has been investigated (see Table). In the cases studied, the alcohols were isolated in high yield. Although phenols could also be protected in this manner, amines were not conveniently masked as their *o*-nitrobenzoyl derivatives.[17] Thus the cyclohexylamide (13; R = NO_2) gave the amine (13; R = NH_2) with a slight excess of zinc dust in aqueous ammonium chloride, whilst with 1 equiv. of zinc dust and ammonium acetate the hydroxylamine (13; R = NH·OH) was obtained. This did not readily liberate cyclohexylamine with base. The amide (14) also gave the amine (15) under the normal reducing conditions.



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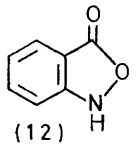

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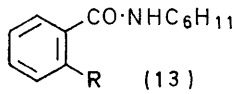

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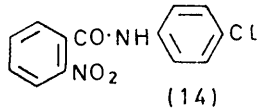

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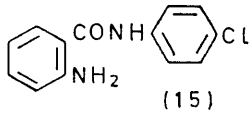

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Use of *o*-nitrobenzoate as a protecting group

Starting material	M.p. (°C)	Reduction product [a]	M.p. (°C)	Isolated yield (%)
(8; Ar = *o*-NO_2·C_6H_4) [b]	149	(4)	115	91
Cholest-5-en-3β-yl *o*-nitrobenzoate [c]	148—149	Cholesterol	148	82
2-Naphthyl *o*-nitrobenzoate [d]	110—112	2-Naphthol	122—123	89
Oestrone *o*-nitrobenzoate [d]	194—195	Oestrone	257—261	92
(13; R = NO_2) [e]	151—152	(13; R = NH_2) [f]	154—155	90
(13; R = NO_2)		(13; R = NH·OH) [g]	149—149·5	50
(14) [h]	183—184	(15) [h]	143—144	90

[a] Generally with zinc and ammonium chloride as the reducing agent. [b] See Experimental section for details. [c] H. Sandquist and J. Gorton, *Svensk farm. Tidskr.*, 1930, **34**, 457. [d] E. B. Barnett and I. G. Nixon, *Chem. News*, 1924, **129**, 190. M. W. Partridge and M. F. C. Stevens, *J. Chem. Soc.*, 1964, 3663. [f] R. R. Clark and E. C. Wagner, *J. Org. Chem.*, 1944, **9**, 55. [g] Treatment with zinc and ammonium acetate gives the hydroxylamine more selectively. [h] U.S.P. 2,643,965/1953.

EXPERIMENTAL

I.r. spectra were recorded with a Unicam SP 200 spectrometer for Nujol mulls, unless otherwise stated, and u.v. with a Unicam SP 800 spectrometer for ethanolic solutions. Mass spectra were determined with an A.E.I. MS9 machine. ^{1}H N.m.r. spectra were recorded with either a Varian T60 or an HA 100 instrument for solutions in deuteriochloroform containing tetramethylsilane as internal reference. Reactions were monitored by t.l.c. on Merck silica gel GF_{254} with ethyl acetate–benzene as solvent. M.p.s were determined with a Kofler hot-stage apparatus. Solutions were dried over anhydrous sodium sulphate.

(1S,5R,6R)-2,2-*Dimethyl*-6-*phenylacetamidopenam*-3α-*yl* m-*Chlorobenzoate* S-*Oxide* (8; Ar = *m*-ClC_6H_4).—(1*S*)-6β-Phenylacetamidopenicillanic acid *S*-oxide (3·50 g) was suspended in dry chloroform (40 ml) and triethylamine (1·02 g) at −20° with stirring while ethyl chloroformate (1·09 g) was added. After 2 h at −20° the solution was cooled to −70° and a solution of *m*-chloroperbenzoic acid (85%; 2·8 g) in dry chloroform (20 ml) was added over 1 h. The mixture was then allowed to warm slowly to room temperature during 16 h, and washed with aqueous sodium hydrogen carbonate (saturated; 2 × 20 ml), 2N-phosphoric acid (2 × 20 ml), and water. After drying, evaporation afforded a white foam (3·74 g, 82%). Preparative t.l.c. gave the m-*chlorobenzoate* (3·0 g, 65%) as a foam, $[\alpha]_D^{24}$ +100·5° (*c* 1·2 in $CHCl_3$), $\nu_{max.}$ 3400, 1800, 1735, 1680, 1500, and 1510 cm^{-1}, τ 2·90 (10H, m, aromatic protons and amide NH), 3·40 (1H, s, 3-H), 4·05 (1H, dd, *J* 4 and 11 Hz, 6-H), 4·90 (1H, d, *J* 4 Hz, 5-H), 6·42 (2H, s, $PhCH_2$), 8·39 (3H, s), and 8·60 (3H, s) (Found: C, 57·3; H, 4·5; Cl, 7·65; N, 5·8; S, 6·9. $C_{22}H_{21}ClN_2O_5S$ requires C, 57·3; H, 4·6; Cl, 7·7; N, 6·1; S, 6·95%).

In a similar run in which the mixture was not kept strictly anhydrous the title compound was obtained (2·3 g, 50%) together with (1*S*,5*R*,6*R*)-2,2-dimethyl-3α-hydroxy-6-phenylacetamidopenam *S*-oxide (4) (0·25 g, 8%), m.p. 126—128° (from MeOH) (lit., 126—128°), and *ethyl* (1S)-6β-*phenylacetamidopenicillanate* S-*oxide* (7; R = Et) (0·30 g, 8%), m.p. 89—90° (from MeOH), $[\alpha]_D^{20}$ +197° (*c* 1·15 in $CHCl_3$), $\nu_{max.}$ 3400, 1780, 1740, and 1690 cm^{-1}, τ 2·69 (5H, s, Ph), 4·06 (1H, dd, *J* 4 and 10 Hz, 6-H), 5·07 (1H, d, *J* 4 Hz, 5-H), 5·44 (1H, s, 3-H), 5·78 (2H, q, *J* 7 Hz), 6·45 (2H, s, CH_2Ph), 8·25 (3H, s), 8·73 (3H, t, *J* 7 Hz), and 8·85 (3H, s) (Found: C, 56·5; H, 5·8; N, 7·4; S, 8·55. $C_{18}H_{22}N_2O_5S$ requires C, 57·1; H, 5·7; N, 7·4; S, 8·4%).

A sample of the title ester was also prepared by esterification of the alcohol (4) (1·0 g) in dry tetrahydrofuran (THF) (10 ml) with *m*-chlorobenzoyl chloride (1·0 g) in dry THF (10 ml) containing pyridine (0·5 g) at 0° for 30 min. The mixture was worked up by chloroform extraction in the normal manner to give, as a foam, the *m*-chlorobenzoate $[\alpha]_D^{24}$ +102° (*c* 0·75 in $CHCl_3$), identical (t.l.c., u.v., and i.r. properties) with the ester prepared before.

(1S,5R,6R)-2,2-*Dimethyl*-6-*phenylacetamidopenam*-3α-*yl* o-*Nitrobenzoate* S-*Oxide* (8; Ar = *o*-NO_2·C_6H_4).—*o*-Nitroperbenzoic acid (98%; 2·2 g) in THF (40 ml) was added to a solution of the mixed anhydride (7; R = CO_2Et) prepared as before from the acid (7; R = H) (3·5 g), at −70°. The mixture was allowed to warm to room temperature overnight and the product was isolated in the usual way. Evaporation of the chloroform extract afforded an amorphous foam which crystallized from methanol as needles

[16] F. Bamberger and F. L. Pyman, *Ber.*, 1909, **42**, 2297.
[17] T. Cohen and W. F. Gray, *J. Org. Chem.*, 1972, **37**, 741.

of the o-*nitrobenzoate* (3·8 g, 80%), m.p. 148·5—149°, $[\alpha]_D^{30}$ +181° (*c* 0·87 in $CHCl_3$), $\nu_{max.}$ 3300, 1800, 1740, and 1685 cm^{-1}, τ 2·00—2·50 (4H, m, *o*-NO_2·C_6H_4), 2·69 (5H, Ph), 2·90 (1H, NH), 3·42 (1H, s, 3-H), 4·00 (1H, dd, *J* 4 and 10 Hz, 6-H), 4·95 (1H, d, *J* 4 Hz, 5-H), 6·40 (2H, s, $PhCH_2$), 8·32 (3H, s), and 8·70 (3H, s) (Found: C, 55·85; H, 4·6; N, 9·15; S, 6·9. $C_{22}H_{21}N_3O_7S$ requires C, 56·0; H, 4·5; N, 8·9; S, 6·8%).

(1S,5R,6R)-2,2-*Dimethyl*-6-*phenylacetamidopenam*-3α-*yl* p-*Nitrobenzoate* S-*Oxide* (8; Ar = *p*-NO_2·C_6H_4).—This was prepared in a similar manner to the *o*-nitrobenzoate. The acid (7; R = H) (3·5 g) with *p*-nitroperbenzoic acid (90%; 2·4 *g*) afforded the title *ester* (3·1 g) (65%) as a non-crystalline foam, $[\alpha]_D^{23}$ +135° (*c* 0·85 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400, 1795, 1730, 1680, 1540, and 1360 cm^{-1}, τ 1·75 (4H, m, *p*-NO_2·C_6H_4), 2·70 (6H, m, Ph and NH), 3·35 (1H, s, 3-H), 3·99 (1H, dd, *J* 4 and 10 Hz, 6-H), 4·85 (1H, d, *J* 4 Hz, 5-H), 6·4 (2H, s, $PhCH_2$), 8·32 (3H, s), and 8·52 (3H, s) (Found: C, 56·5; H, 4·8; N, 8·8; S, 6·9. $C_{22}H_{21}N_3O_7S$ requires C, 56·0; H, 4·5; N, 8·9; S, 6·8%).

(1S,5R,6R)-2,2-*Dimethyl*-6-*phenylacetamidopenam*-3α-*yl* 2,4-*Dinitrobenzoate* S-*Oxide* [8; Ar = 2,4-$(NO_2)_2C_6H_4$].—The alcohol (4) (1·0 g) in anhydrous THF (10 ml) was treated with 2,4-dinitrobenzoyl chloride (3 equiv.) in benzene (15 ml) containing pyridine (1·0 ml) at 0 °C. The mixture was allowed to warm to room temperature during 15 h, poured into water, and extracted with ethyl acetate. The organic layer was washed with aqueous sodium carbonate (3% w/v; 2 × 20 ml), 2N-phosphoric acid (2 × 20 ml), and water (20 ml) before drying and evaporation. The resultant foam crystallized from methanol to give the 2,4-*dinitrobenzoate* (0·95 g, 60%), m.p. 160—161°, $[\alpha]_D^{29}$ +161·5° (*c* 0·89 in $CHCl_3$), $\nu_{max.}$ 3400, 1800, 1740, 1680, 1540, and 1360 cm^{-1}, τ 1·1—2·1 (3H, m aromatic), 2·70 (5H, m, Ph), 2·90br (1H, d, NH), 3·40 (1H, s, 3-H), 3·98 (1H, dd, *J* 4 and 10 Hz, 6-H), 4·90 (1H, d, *J* 4 Hz, 5-H), 6·40 (2H, s, CH_2Ph), 8·35 (3H, s), and 8·73 (3H, s) (Found: C, 50·9; H, 4·0; N, 10·45; S, 6·4. $C_{22}H_{20}N_4O_9S$ requires C, 51·2; H, 3·9; N, 10·8; S, 6·2%).

(1S,5R,6S)-2,2-*Dimethyl*-6-*phenylacetamidopenam*-3α-*yl* m-*Chlorobenzoate* S-*Oxide* (9; Ar = *m*-ClC_6H_4).—The 6*R*-epimer (8; Ar = *m*-ClC_6H_4) (0·46 g) in anhydrous THF (5 ml) was treated with dry diethylamine (0·2 ml) at room temperature. After 3 h ^1H n.m.r. data and t.l.c. indicated that equilibrium had essentially been reached. The mixture was poured into 2N-phosphoric acid (25 ml) and extracted with ethyl acetate (2 × 10 ml). The organic layer was washed with water (2 × 10 ml), dried, and evaporated to dryness. ^1H N.m.r. analysis indicated a 1 : 1 ratio of the 6*R*- and 6*S*-epimers. The title compound was separated by preparative t.l.c. as an amorphous solid (0·18 g, 40%). The (6S)-*ester* had $[\alpha]_D^{22}$ +74° (*c* 1·1 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400, 1795, 1730, and 1680 cm^{-1}, τ 2·00—3·00 (9H, aromatic), 3·35 (1H, d, *J* 8 Hz, NH), 3·50 (1H, s, 3-H), 4·72 (1H, d, *J* 2 Hz, 5-H), 5·08 (1H, dd, *J* 2 and 8 Hz, 6-H), 6·42 (2H, s, $PhCH_2$), 8·40 (3H, s), and 8·59 (3H, s) (Found: C, 57·5; H, 4·9; N, 5·7; S, 6·6. $C_{22}H_{21}ClN_2O_5S$ requires C, 57·3; H, 4·6; N, 6·1; S, 6·95%).

In a similar manner, the starting epimer (8; Ar = *m*-ClC_6H_4) was treated with triethylamine, 2,2,6,6-tetramethylpiperidine, or di-isopropylethylamine, the reactions being followed by ^1H n.m.r. spectroscopy and t.l.c. In each case epimerization occurred but the rates were extremely low.

Treatment of the product 6S-epimer (9; Ar = *m*-ClC_6H_4) with diethylamine in anhydrous THF at room temperature rapidly re-established a 1 : 1 equilibrium with the 6*R*-epimer. Appropriate t.l.c. and ^1H n.m.r. assays indicated that equilibration was reached within 30 min.

Methyl (1S)-6α-*Phenylacetamidopenicillanate* S-*Oxide* (10).—The ester (7; R = Me) (0·5 g) was treated with diethylamine (0·2 ml) in tetrahydrofuran (5 ml) at room temperature for 6 h. Preparative t.l.c. afforded the *title ester* (0·2 g, 40%), as needles, m.p. 153—154° (from MeOH), $[\alpha]_D^{20}$ +188° (*c* 0·95 in $CHCl_3$), $\nu_{max.}$ 3400, 1780, 1740, and 1680 cm^{-1}, τ 2·70 (6H, Ph and NH), 4·80 (2H, m, 5-H and 6-H), 5·52 (1H, s, 3-H), 6·21 (3H, s, MeO), 6·40 (2H, s, $PhCH_2$), 8·38 (3H, s), and 8·85 (3H, s) (Found: C, 55·45; H, 5·7; N, 7·3; S, 8·5. $C_{17}H_{20}N_2O_5S$,0·5MeOH requires C, 55·2; H, 5·8; N, 7·3; S, 8·4%).

(1S,5R,6S)-2,2-*Dimethyl*-6-*phenylacetamidopenam*-3α-*yl* p-*Nitrobenzoate* S-*Oxide* (9; Ar = *p*-NO_2·C_6H_4).—In a similar manner to the *m*-chlorobenzoate, the *p*-nitrobenzoate (8; Ar = *p*-NO_2·C_6H_4) (10·47 g) was treated with diethylamine (0·2 ml) in anhydrous THF (5 ml) at room temperature for 3 h. Work-up in the usual manner produced the *ester* (0·20 g, 43%) as an amorphous solid, $[\alpha]_D^{30}$ +78·3° (*c* 1·3 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400, 1795, 1730, and 1680 cm^{-1}, τ 1·70—2·00 (4H, m, aromatic), 2·20 (5H, m, Ph), 3·27 (1H, d, *J* 7 Hz, NH), 3·50 (1H, s, 3-H), 4·69 (1H, d, *J* 2 Hz), 5·13 (1H, dd, *J* 2 and 7 Hz, 6-H), 6·50 (2H, s, $PhCH_2$), 8·44 (3H, s), and 8·58 (3H, s), τ (C_6D_6) 2·20—2·50br (4H, s, aromatic), 2·96 (5H, s, aromatic), 3·30 (1H, s, 3-H), 4·05br (1H, d, NH), 4·97 (1H, d, *J* 2 Hz, 5-H), 5·18 (1H, dd, *J* 2 and 7 Hz, 6-H), 6·81 (2H, s, CH_2Ph), 8·76 (3H, s), and 9·14 (3H, s) (Found: C, 55·9; H, 4·7; N, 9·0; S, 6·8. $C_{22}H_{21}N_3O_7S$ requires C, 56·0; H, 4·5; N, 8·9; S, 6·8%).

(1S,5R,6S)-2,2-*Dimethyl*-6-*phenylacetamidopenam*-3α-*yl* o-*Nitrobenzoate* S-*Oxide* (9; Ar = *o*-NO_2·C_6H_4).—The 6*R*-isomer (8; Ar = *o*-NO_2·C_6H_4) (0·47 g) was treated with imidazole (0·15 g) in anhydrous THF (10 ml) at room temperature. A 1 : 1 ratio of the two epimers was reached after 24 h (t.l.c. assay). Ethyl acetate (25 ml) was added and the organic solution extracted with 2N-phosphoric acid (2 × 20 ml) and water (20 ml), and then dried. Evaporation afforded the epimeric mixture, which was separated by preparative t.l.c. to yield the *title compound* (0·17 g, 38%) as a crystalline solid, m.p. 157—158° (from acetone–chloroform), $[\alpha]_D^{23}$ +186·5° (*c* 0·89 in $CHCl_3$), $\nu_{max.}$ 3250, 1780, 1740, 1680, 1540, and 1360 cm^{-1}, τ 1·9—2·4 (4H, m, aromatic), 2·65 (5H, m, Ph), 3·15 (1H, d, *J* 8 Hz, NH), 3·45 (1H, s, 3-H), 4·68 (1H, d, *J* 2 Hz, 5-H), 5·00 (1H, dd, *J* 2 and 8 Hz, 6-H), 6·35 (2H, s, $PhCH_2$), 8·35 (3H, s), and 8·68 (3H, s) (Found: C, 56·0; H, 4·6; N, 8·6; S, 7·0. $C_{22}H_{21}N_3O_7S$ requires C, 56·0; H, 4·5; N, 8·9; S, 6·8%). This epimerization was also effected, much more rapidly, with diethylamine in the manner previously described.

Photolysis of (1S,5R,6R)-2,2-*Dimethyl*-6-*phenylacetamidopenam*-3α-*yl* 2,4-*Dinitrobenzoate* S-*Oxide* [8; Ar = 2,4-$(NO_2)_2C_6H_3$].—The ester (0·52 g) in 1 : 1 water–THF (20 ml) was photolysed through a Pyrex filter under nitrogen with a Phillips 125 W medium-pressure mercury lamp. After 6 h, when most of the starting material had disappeared, chloroform (50 ml) was added and the organic layer extracted with aqueous sodium hydrogen carbonate (5% w/v; 2 × 25 ml) and water (25 ml) before drying. Preparative t.l.c. afforded the alcohol (4) (0·065 g, 20%), m.p. 126—128° (from MeOH), identical with an authentic sample.

Reduction with Sodium Borohydride of the 2,4-*Dinitrobenzoate* [8; Ar = 2,4-$(NO_2)_2C_6H_3$].—The ester (0·52 g) in

methanol (10 ml) at 0° was reduced with sodium borohydride (0·10 g). After 5 min glacial acetic acid was added to quench the reaction (to pH 7). The products were extracted with ethyl acetate and separated by preparative t.l.c. to give the carbinol (11) (0·082 g, 25%), identical with a sample prepared by reduction with sodium borohydride of the alcohol (4).

Reduction of o-*Nitrobenzoates*.—The general procedure was as follows. The *o*-nitrobenzoate (1 equiv.) in THF at 0° was stirred with ammonium chloride (7 equiv.) in water, the volume of solvent being adjusted to give a homogeneous solution. Zinc dust (2·1 equiv.) was added slowly, in portions, to the vigorously stirred mixture. The reactions were monitored by t.l.c. After disappearance of the starting material (0·5—2 h) the mixture was filtered and the solids washed with ethyl acetate and water. The filtrate was extracted with ethyl acetate, and the benzisoxazolinone was washed out with aqueous sodium hydrogen carbonate solution. The extract was dried and evaporated to give the alcohol, or phenol, in essentially quantitative yield. Ammonium acetate could also be used in place of the chloride.

Oestrone o-*Nitrobenzoate*.—Prepared from *o*-nitrobenzoyl chloride and oestrone in pyridine, this *ester* had m.p. 194—195° (from MeOH), $[\alpha]_D^{20}$ +104° (*c* 1·1 in dioxan), $\nu_{max.}$ 1740 and 1720 cm^{-1} (Found: C, 71·5; H, 6·0; N, 3·3. $C_{25}H_{25}NO_5$ requires C, 71·6; H, 6·0; N, 3·3%).

N-*Cyclohexyl*-o-(*hydroxyamino*)*benzamide* (13; R = NH·OH).—Reduction of the *o*-nitrobenzamide (13; R = NO_2) with zinc and ammonium acetate gave the *hydroxylamine* (70%), m.p. 148—149·5°, $\nu_{max.}$ 3280, 3100, 1620, 1600, and 1540 cm^{-1} (Found: C, 66·8; H, 7·8; N, 12·1. $C_{13}H_{18}N_2O_2$ requires C, 66·6; H, 7·7; N, 12·0%).

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