Preparation of Secopenicillanates; Preparation of Methyl 3-Methyl-2-[(2*R*,3*R*)-2-methylthio-4-oxo-3-phthalimidoazetidin-1-yl]but-2-enoate

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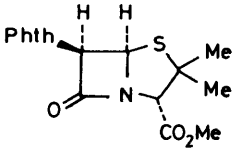
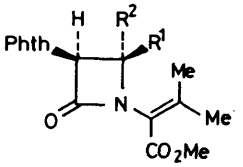
Treatment of methyl (1*R*,6*R*)-1-oxo-6-phthalimidopenicillanate (4) with trimethyl phosphite gives a mixture of bis-{(2*R*,3*R*)-1-[(1*R*)-1-methoxycarbonyl-2-methylprop-2-enyl]-4-oxo-3-phthalimidoazetidin-2-yl} disulphide (12) (25—60%) and methyl (2*R*)-3-methyl-2-[(2*R*,3*R*)-2-methylthio-4-oxo-3-phthalimidoazetidin-1-yl]but-3-enoate (11) (15—35%). The latter compound was also prepared by heating methyl (1*R*,6*R*)-1-oxo-6-phthalimidopenicillanate sulphoxide in 2-methylpropane-1-thiol, under reflux, to give the unsymmetrical disulphide (21) which was cleaved by trimethyl phosphite to give the non-conjugated secopenicillanate (11). Conversion of the non-conjugated secopenicillanate (11) into methyl 3-methyl-2-[(2*R*,3*R*)-2-methylthio-4-oxo-3-phthalimidoazetidin-1-yl]but-2-enoate (2) was achieved using a catalytic amount of diazabicyclononene (DBN) at room temperature. Prolonged treatment with DBN under reflux in benzene, gave a mixture of the conjugated secopenicillanate (2) and its 3'-epimer (22) in a ratio of 3 : 7.

ATTEMPTS to isolate a sulphonium salt from the reaction between methyl 6β-phthalimidopenicillanate (1) and trimethyloxonium tetrafluoroborate were unsuccessful. However, it was found that treatment of the crude alkylation product mixture with anhydrous sodium carbonate led to the isolation of a 2.5 : 1 mixture of β-lactams that were tentatively identified as the *cis*- and *trans*-phthalimidosecopenicillanates (2) and (3).[1] In



(1)



(2) R^1 = SMe, R^2 = H
(3) R^1 = H, R^2 = SMe

Phth = phthalimido

order to confirm the structures of these compounds, it was decided to prepare an authentic sample of the *cis*-isomer (2), and to study its epimerization.

Secopenicillanate (2) has been mentioned briefly in the literature.[2] It was prepared by heating a solution of methyl 1-oxo-6β-phthalimidopenicillanate (4) in benzene under reflux in the presence of a silylating agent to give the protected sulphenic acid (5). Isomerization of (5) using triethylamine, and reduction by trimethyl phosphite, gave a mixture of methyl 6β-phthalimidopenicillanate (1) and the *cis*-phthalimidosecopenicillanate (2). However, no details of the reactions, or yields, were reported.[2] The closely related non-conjugated secopenicillanate (7) has been prepared by heating a solution of trichloroethyl 1-oxo-6β-phthalimidopenicillanate (6) and trimethyl phosphite in benzene under reflux.[3] Phosphorus-containing side-products were also isolated, but again no details of the reaction have been reported.[3] The phenylacetamidosecopenicillanate (10) has been prepared by heating a solution of the 1-oxopenicillanate (8) in 2-methylpropane-1-thiol to give the disulphide (9) which was cleaved by trimethyl phosphite,[4] and seco-

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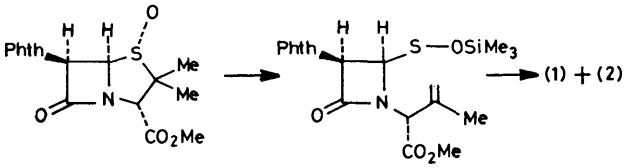
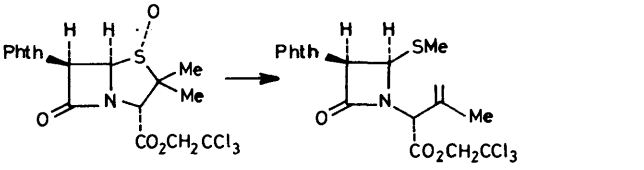
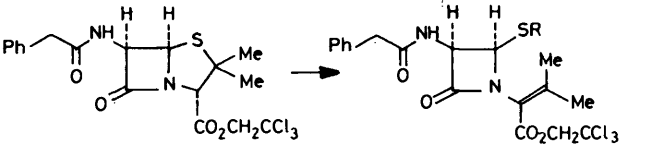
penicillanates have been prepared by treatment of the parent penicillanates with sodium hydride and a reactive alkyl halide. However, this latter procedure is limited



(4) (5) (1) + (2)



(6) (7)



(8)

(9) R = Me_2CHCH_2S
(10) R = Me

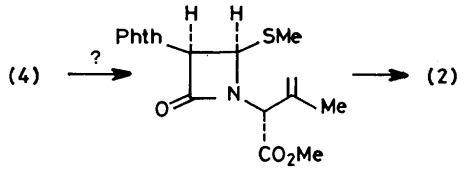
to 6,6-dibromo- and 6β-tritylamino-penicillanates.[5]

It was decided to prepare secopenicillanate (2) by treatment of methyl 1-oxo-6β-phthalimidopenicillanate (4) with trimethyl phosphite. By analogy with the formation of the non-conjugated secopenicillanate (7), this should give methyl ester (11), which could be isomerized to the desired secopenicillanate (2) by base.

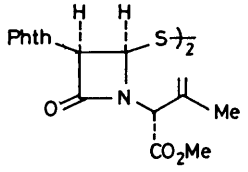
When sulphoxide (4) was heated in benzene under reflux in the presence of trimethyl phosphite, two products were isolated. The first, isolated by crystallization of the crude product mixture, was identified as the symmetrical azetidinyl disulphide (12). The second, isolated by chromatography of the residue, was the desired non-conjugated secopenicillanate (11).

These products were identified on the basis of their

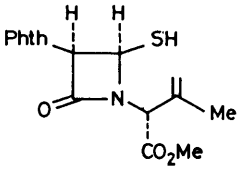
spectroscopic data. The ^1H n.m.r. spectrum of disulphide (12) resembles that reported for the monomeric thiol (13),[6] except for the SH peak which is missing. Moreover our product was a crystalline solid, m.p. 112.5—113 °C, whereas thiol (13) is described as an oil.



(11)



(12)



(13)

Our product did not show an SH band in its i.r. spectrum, but it did have a molecular ion, *m/e* 718, in its mass spectrum.

The yields of disulphide (12) and secopenicillanate (11) were found to depend upon the reaction time as shown in the Table. The yield of disulphide (12) decreases, and the yield of secopenicillanate (11) increases, the longer the reaction is continued.

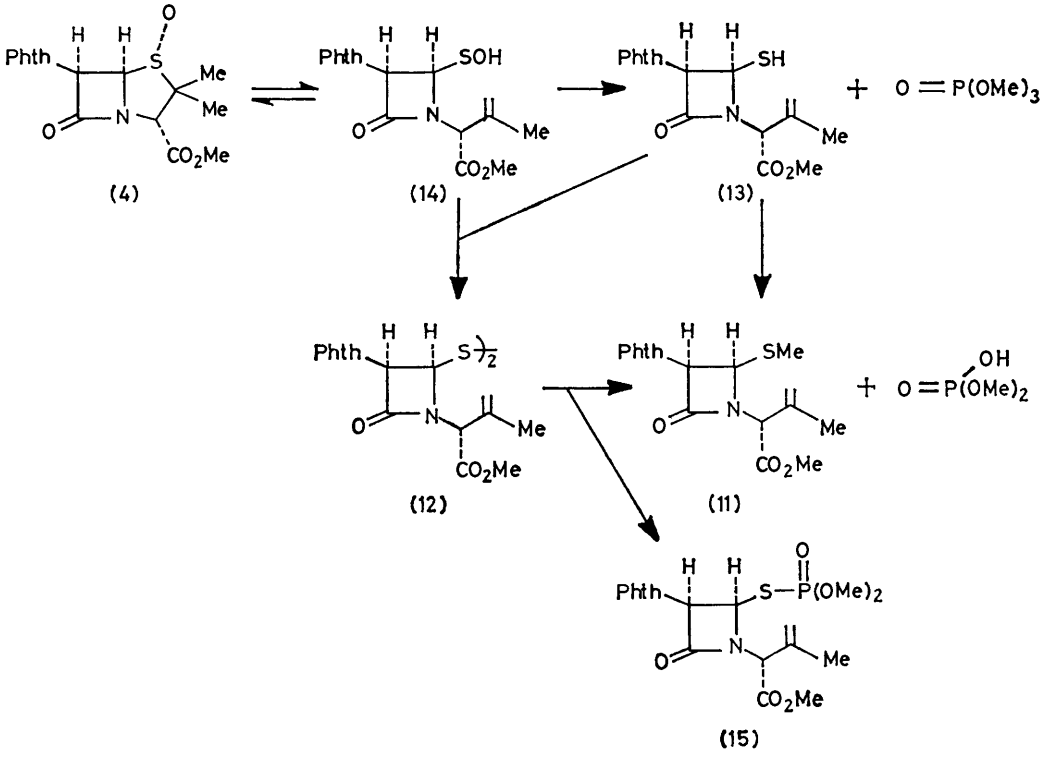
One explanation for the formation of disulphide (12) is given in the Scheme. It is suggested that sulphenic acid (14), known to be in equilibrium with sulphoxide (4)

Yields [a] of compounds (11) and (12) on treatment of sulphoxide (4) with trimethyl phosphite

Reaction time	Yield (%) of disulphide (12)	Yield (%) of secopenicillanate (11)	Unchanged sulphoxide (4)
30 min	45	15	30
3 h	40—60	15—20	
60 h	25	35	

[a] Yields estimated by ^1H n.m.r. of the crude product mixtures.

in refluxing benzene,[7] is reduced by trimethyl phosphite to thiol (13). The thiol (13) then reacts by two pathways. Either it condenses with more sulphenic acid (14) to give disulphide (12), or it is methylated by trimethyl phosphate to give the secopenicillanate (11). The disulphide (12) is unstable under the reaction conditions, and is slowly cleaved by trimethyl phosphite to give the secopenicillanate (11), and the sulphur–phosphorus compound (15), which was not isolated in our work, but is analogous to compounds isolated by Cooper.[3] Alternatively the disulphide (12) may have been formed by atmospheric oxidation of the intermediate thiol (13) during work-up of the reaction (the reaction itself was carried out under nitrogen), but this mechanism would not explain the formation of Cooper's sulphur–phosphorus compounds.[3] Disulphides related to the symmetrical azetidinyl disulphide (12) have been reported in the literature. For example, treatment of thiosulphonate (16) with sodium azide gave disulphide (17),[8] and the unsymmetrical disulphide (18) was converted into the symmetrical disulphide (19) in aqueous base.[9]



SCHEME

A second synthesis of azetidinyl disulphide (12) was briefly examined. Methyl 1-oxo-6β-phthalimidopenicillanate (4) was heated under reflux in benzene in the presence of 2-mercaptobenzothiazole [9] to afford a 65% yield of the crystalline disulphide (20). Reduction of disulphide (20) with sodium borohydride in diglyme at −50 °C, followed by low-temperature quenching using methanol and acetic acid, gave an oil which was fractionally crystallized to give 3-mercaptobenzothiazole (71%), and the symmetrical azetidinyl disulphide (12) (19%) identical with the sample prepared above. Presumably this reduction proceeds by way of thiol (13) which is oxidized during the crystallization process. No attempt was made to isolate thiol (13), and an attempt to trap it by alkylation with methyl iodide was unsuccessful.

A second synthesis of the non-conjugated secopenicillanate (11) was examined, and found to be more efficient. Methyl 1-oxo-6β-phthalimidopenicillanate (4) was heated in 2-methylpropane-1-thiol under reflux for 16 h to give the azetidinyl isobutyl disulphide (21) in 63% yield after column chromatography. Cleavage of this disulphide with trimethyl phosphite in benzene gave the desired non-conjugated secopenicillanate (11) in 64% isolated yield.

Treatment of the non-conjugated secopenicillanate (11) with DBN in chloroform at 20 °C rapidly gave the conjugated isomer (2). Under these conditions, no epimerization of the β-lactam substituents was observed, and secopenicillanate (2) was isolated as a recrystallized product in 58% yield. The sample prepared in this way was identified from its spectroscopic data, and was found to be identical with the sample prepared by treatment of methyl 6β-phthalimidopenicillanate (1) with trimethyloxonium tetrafluoroborate and sodium carbonate.

Finally it was decided to study the epimerization of the *cis*-phthalimidosecopenicillanate (2) in base. When a solution of secopenicillanate (2) and DBN in benzene was heated under reflux for 19 h,[10] a mixture of secopenicillanates (2) and (22) was obtained, in the ratio 3 : 7. This ratio did not change on further heating, and so a sample of the *trans*-isomer (22) was crystallized out of the reaction mixture for characterization. It was identified on the basis of its spectroscopic data, and was found to be identical with a sample prepared by treatment of methyl 6α-phthalimidopenicillanate (23) with trimethyloxonium tetrafluoroborate and sodium carbonate.[1]

EXPERIMENTAL

General details are given in the preceding paper.[1]

Treatment of Methyl (1R,6R)-1-*Oxo*-6-*phthalimidopenicillanate* (4) *with Trimethyl Phosphite*.—Methyl (1*R*,6*R*)-1-oxo-6-phthalimidopenicillanate (4) (0.5 g) [11] and trimethyl phosphite (0.34 ml) were dissolved in anhydrous benzene, and the solution heated under reflux under dry nitrogen for 3 h. The mixture was then diluted with dichloromethane (40 ml), washed with water (50 ml), dried ($MgSO_4$), and concentrated *in vacuo* to leave a light brown oil. Crystallization from chloroform–hexane gave crystals of *bis*-{(2*R*,3*R*)-1-[(1*R*)-1-*methoxycarbonyl*-2-*methylprop*-2-*enyl*]-4-*oxo*-3-*phthalimidoazetidin*-2-*yl*} *disulphide* (12) (148 mg), m.p. 112.5—113 °C, $[\alpha]_D$ −386° (0.015M in $CHCl_3$), $\nu_{max.}$ (Nujol) 1 775, 1 725, 1 120, 920, and 720 cm^{-1}, δ($CDCl_3$) 1.96 (3 H, s, CH_3), 3.70 (3 H, s, OCH_3), 4.93 (1 H, m, vinylic H), 4.97 (1 H, s, H-1′), 5.19 (1 H, m, vinylic H), 5.43 (1 H, d, *J* 4.9 Hz, H-3), 5.68 (1 H, d, *J* 4.9 Hz, H-2), and 7.8 (4 H, m, aromatic H); *m/e* 718 (M^+), 358 ($M^+ - C_{17}H_{16}N_2O_5S$), 299 ($M^+ - C_{19}H_{19}N_2O_7S$), and 214 ($M^+ - C_{25}H_{18}N_3O_7S$) (Found: C, 56.55; H, 4.15; N, 7.7. $C_{34}H_{30}N_4O_{10}S_2$ requires C, 56.8; H, 4.2; N, 7.8%). The mother-liquor from the crystallization was concentrated, and chromatographed on silica (35 g) (eluted with ethyl acetate–benzene, 3 : 7) to give *methyl* (2R)-3-*methyl*-2-[(2*R*,3*R*)-2-*methylthio*-4-*oxo*-3-*phthalimidoazetidin*-1-*yl*]*but*-3-*enoate* (11) (83 mg), as an oil, homogeneous by t.l.c., $\nu_{max.}$ ($CHCl_3$) 1 770, 1 730, 1 620, and 1 220 cm^{-1}, δ($CDCl_3$) 2.07 (3 H, s, SCH_3), 2.10br (3 H, s, CH_3), 3.81 (3 H, s, OCH_3), 4.99 (1 H, m, vinylic H), 5.11 (1 H, m, vinylic H), 5.14 (1 H, s, H-2), 5.50 (1 H, d, *J* 5 Hz, H-3′), 5.67 (1 H, d, *J* 5 Hz, H-2′), and 7.80 (4 H, m, aromatic H); *m/e* 374 (M^+), 359 ($M^+ - CH_3$), 327 ($M^+ - SCH_3$), 315 ($M^+ - CO_2CH_3$), 219 [$M^+ - CH_3C(CH_2)\cdot CH(CO_2CH_3)\cdot NCO$], and 187 ($M^+$ — PhthCHCO).

When the above reaction was repeated, with the period of reflux being extended to 65 h, a higher yield (110 mg) of chromatographed secopenicillanate (11) was obtained.

Benzothiazol-2-yl {(2*R*,3*R*)-1-[(1*R*)-1-*Methoxycarbonyl*-2-*methylprop*-2-*enyl*]-4-*oxo*-3-*phthalimidoazetidin*-2-*yl*} *Disulphide* (20).—A solution of methyl (1*R*,6*R*)-1-oxo-6-phthalimidopenicillanate (4) (1.0 g) and 2-mercaptobenzothiazole (0.44 g) in anhydrous benzene (10 ml) was heated under reflux under dry nitrogen for 90 min. Concentration *in vacuo*, and recrystallization from aqueous methanol gave *benzothiazol*-2-*yl* {(2*R*,3*R*)-1-[(1*R*)-1-*methoxycarbonyl*-2-*methylprop*-2-*enyl*]-4-*oxo*-3-*phthalimidoazetidin*-2-*yl disulphide* (20) (0.9 g) as crystals, m.p. 100—101.5 °C, $[\alpha]_D$ −182° (0.073M in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 1 770, 1 730, and 1 620 cm^{-1}; δ($CDCl_3$) 2.10br (3 H, s, CH_3), 3.81 (3 H, s, OCH_3), 5.11 (2 H, s, and overlapping m, vinylic H and H-1'), 5.25 (1 H, m, vinylic H), 5.85 (2 H, s, H-2 and H-3), and 7.0—8.0 (8 H, complex m, aromatic H); δ([$^2H_6$]acetone) 2.08 (3 H, s, CH_3), 3.81 (3 H, s, OCH_3), 5.1—5.4 (3 H, overlapping m, vinylic H and H-1'), 5.90 and 5.98 (each 1 H, d, *J* 4.5 Hz, H-2 and -3), and 7.3—8.1 (8 H, complex m, aromatic H) (Found: C, 54.65; H, 3.7; N, 7.9; S, 18.2. $C_{24}H_{19}N_3O_5S_2$ requires C, 54.85; H, 3.65; N, 8.0; S, 18.3%).

Reduction of Disulphide (20).—Sodium borohydride (15 mg) was added to a solution of disulphide (20) (400 mg) in anhydrous diglyme (3 ml) under nitrogen at −50 °C. After 30 min a solution of methanol (500 mg) and glacial acetic acid (30 mg) in dichloromethane (3 ml) was added, and the mixture allowed to warm up to 20 °C. The mixture was then washed with water, dried ($MgSO_4$), and rigorously concentrated *in vacuo* to leave an oil. Trituration of this oil with warm diethyl ether, and concentration *in vacuo* of the ether extract, gave 2-mercaptobenzothiazole (90 mg). The residue was then dissolved in ethyl acetate–diethyl ether, and cooled, to give the symmetrical azetidinyl disulphide (12) (50 mg) as crystals, identical (^1H n.m.r., i.r., t.l.c., m.p.) with the sample prepared as described above.

Methyl 3-*Methyl*-2-[(2*R*,3*R*)-2-*methylthio*-4-*oxo*-3-*phthalimidoazetidin*-1-*yl*]*but*-2-*enoate* (2).—Methyl (1*R*,6*R*)-1-oxo-6-phthalimidopenicillanate (4) (1.8 g) was dissolved in freshly distilled 2-methylpropane-1-thiol (20 ml), and the solution heated under reflux under dry nitrogen for 16 h. Concentration *in vacuo* gave an oil that was chromatographed on silica (100 g) (eluted with ethyl acetate–hexane) to give {(2*R*,3*R*)-1-[(1*R*)-1-*methoxycarbonyl*-2-*methylprop*-2-*enyl*]-4-*oxo*-3-*phthalimidoazetidin*-2-*yl*} 2-*methylpropyl disulphide* (21) (1.4 g) as a brown foam, homogeneous by t.l.c., $\nu_{max.}$ ($CHCl_3$) 1 780 and 1 720 cm^{-1}, δ($CDCl_3$) 0.85 and 0.89 [each 3 H, d, *J* 7 Hz, $CH(CH_3)_2$], 1.7 [1 H, m, $CH(CH_3)_2$], 2.07br (3 H, s, $\equiv C-CH_3$), 2.4 (2 H, m, SCH_2), 3.89 (3 H, s, OCH_3), 5.15 and 5.27 (3 H, overlapping m, vinylic H and H-1'), 5.67 and 5.73 (each 1 H, d, *J* 5 Hz, H-2 and -3), and 7.9 (4 H, complex m, aromatic H); *m/e* 448 (M^+), 420 ($M^+ - CO$), 389 ($M^+ - CO_2CH_3$), 359 ($M^+ - C_4H_9S$), 327 ($M^+ - C_4H_9S_2$), and 299 ($M^+ - C_4H_9SH$, CO_2CH_3).

Disulphide (21) was not purified further; instead a portion (450 mg) was dissolved in anhydrous benzene, trimethyl phosphite (250 mg) was added, and the solution heated under reflux under dry nitrogen for 30 min. Concentration *in vacuo* gave an oil that was suspended in hexane, and the hexane suspension stirred at 20 °C for 16 h. This gave a two-phase mixture of an oil and a hexane solution. The hexane solution was decanted off, and concentrated to give dimethyl isobutyl thiophosphate (220 mg), δ($CDCl_3$) 1.02 (6 H, d, *J* 7 Hz, 2 × CH_3), 1.6—2.3 (1 H, m, CH), 2.74 (2 H, dd, *J* 6 and 13 Hz, CH_2), and 3.79 (6 H, d, *J* 13 Hz, OCH_3). The residual oil (410 mg) was purified by chromatography on silica (30 g) (eluted with ethyl acetate–hexane) to give methyl (2*R*)-3-methyl-2-[(2*R*,3*R*)-2-methylthio-4-oxo-3-phthalimidoazetidin-1-yl]but-3-enoate (11) (240 mg) as a foam, identical (n.m.r., i.r., t.l.c.) with the sample prepared as described above.

A portion (120 mg) of the non-conjugated secopenicillanate (11) prepared above, was dissolved in anhydrous dichloromethane (3 ml) and DBN (2 mg) added. The solution was stirred for 30 min at 20 °C, before being quenched by the addition of dilute aqueous acetic acid (3 ml). The two layers were separated, and the organic layer washed twice with dilute aqueous acetic acid, and once with water, dried ($MgSO_4$), and concentrated *in vacuo* to give a solid (70 mg) that was recrystallized from diethyl ether–cyclohexane to give *methyl* 3-*methyl*-2-[(2*R*,3*R*)-2-*methylthio*-4-*oxo*-3-*phthalimidoazetidin*-1-*yl*]*but*-2-*enoate* (2), as fine needle-like crystals, m.p. 167—168 °C, $[\alpha]_D$ −0.02° (0.003 2M in $CHCl_3$), $\nu_{max.}$ (Nujol) 1 790, 1 778, 1 720, 1 630, 1 230, 1 120, 928, and 914 cm^{-1}; δ($CDCl_3$) 2.03 (3 H, s, SCH_3), 2.30 and 2.33 (each 3 H, s, CH_3), 3.81 (3 H, s, OCH_3), 5.31 and 5.69 (each 1 H, d, *J* 5 Hz, H-2' and -3'), and 7.85 (4 H, complex m, aromatic H) (Found: C, 57.95; H, 5.05; N, 7.5; S, 8.8. $C_{18}H_{18}N_2O_5S$ requires C, 57.75; H, 4.85; N, 7.5; S, 8.55%).

Epimerization of Methyl 3-*Methyl*-2-[(2R,3R)-2-*methylthio*-4-*oxo*-3-*phthalimidoazetidin*-1-*yl*]*but*-2-*enoate* (2).—The *cis*-phthalimidosecopenicillanate (2) (100 mg) and DBN (6 mg) were dissolved in [$^2H_6$]benzene (2 ml), and the mixture heated under reflux for 19 h. The ^1H n.m.r. spectrum of the reaction mixture at this time showed the presence of the *cis*- and *trans*-phthalimidosecopenicillanates (2) and (22) in the ratio 3 : 7, and this ratio did not change appreciably when reflux was continued for a further 16 h. The mixture was then diluted with dichloromethane (10 ml), washed with dilute aqueous acetic acid (2 × 10 ml) and water (10 ml), dried ($MgSO_4$), and concentrated *in vacuo* to give a mixture of *cis*- and *trans*-phthalimidosecopenicillanates (2) and (22) (73 mg) in the ratio 3 : 7 (^1H n.m.r.). Crystallization of this mixture from acetone–hexane gave a sample of pure *trans*-phthalimidosecopenicillanate (22) (18 mg) identical (^1H n.m.r., i.r., m.p.) with the material obtained from methyl (6*S*)-6-phthalimidopenicillanate by treatment with trimethyloxonium tetrafluoroborate and sodium carbonate.[1]

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