Studies Related to Penicillins and Cephalosporins. Part 5.[1] A New Relay Synthesis of Penicillin

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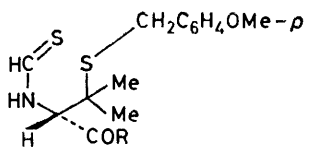
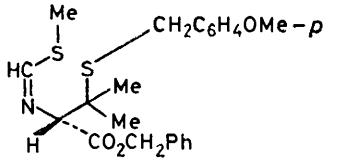
3-Azido-1-(1-benzyloxycarbonyl-2-*p*-methoxybenzylthio-2-methylpropyl)-4-methylthioazetidin-2-one (4) was converted into benzyl (±)-6-azido-6-*epi*-penicillanate (6), and its stereoisomer (7) was converted into benzyl (±)-6-azido-5-*epi*-penicillanate (9) and benzyl (±)-6-azido-penicillanate (10). The synthesis involved a regiospecific chlorinolysis of the two sulphide bonds in (4) and in (7), followed by reductive cyclization of the resulting dichloro-compounds with tin(II) chloride. 3-*p*-Methoxybenzylthiovaline was used as starting material for the preparation of the key compounds (4) and (7), by a route involving the construction of the β-lactam ring on the nitrogen atom of the amino-acid.

DESPITE wide interest in the synthesis of β-lactam antibiotics,[2] only three total syntheses of penicillin have been reported. Each of these syntheses can be characterized by the bond, or bonds, involved in the key step in which the penam backbone is completed. In Sheehan's[3] classical synthesis the bicyclic β-lactam system is obtained through formation of the 4,7-amide bond. Merck's[4] total synthesis involves a cycloaddition reaction,[5] by which the 4,7- and the 5,6-bonds are formed.[6] In Baldwin's[7] stereospecific synthesis closure to the fused bicyclic system is effected through the formation of the 1,2-carbon to sulphur bond. In a



(1) R = OH·HN(C$_6$H$_{11}$)$_2$
(2) R = OCH$_2$Ph



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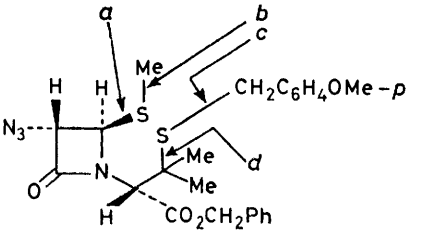

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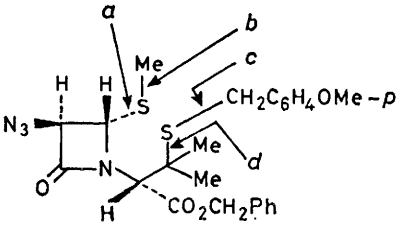

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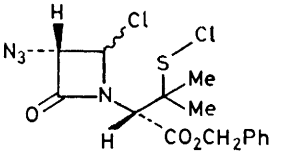

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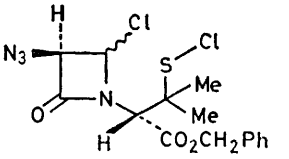

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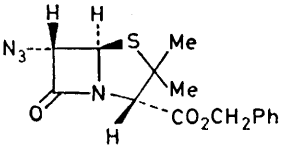

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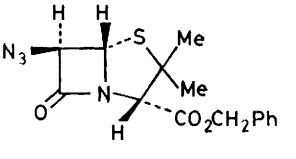

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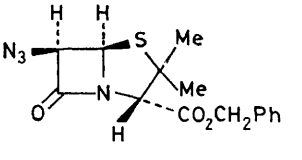

(10)

preliminary communication we have reported the syntheses of (±)-penicillin and (±)-2-spirocyclopentanobisnorpenicillin systems by a route in which the penam nucleus is completed through the formation of the 1,5-bond.[8] This synthetic route is now described in detail for the preparation of three isomers of benzyl (±)-6-azidopenicillanate. Since the 6α-azido-isomer has been previously converted into penicillin G,[4] a new relay total synthesis of (±)penicillin G is thus presented.

RESULTS AND DISCUSSION

Extending a synthetic strategy described in previous papers of this series,[1] the β-lactam ring was built on the nitrogen atom of an α-aminocarboxylic acid bearing a functional group on its side-chain. Thus, 3-*p*-methoxybenzylthiovaline was condensed with *O*-ethyl thionoformate and the thioformamide so formed was isolated as its dicyclohexylammonium salt (1).[9] The benzyl ester (2), obtained from the salt (1) and benzyl bromide in dimethylformamide, was treated with methyl iodide and potassium carbonate in acetone to give the methylthioformimidate (3). Reaction of (3) with azidoacetyl chloride and triethylamine afforded a mixture of the two *trans*-β-lactams (4) * and (7).*

The substituents on the two sulphur atoms were carefully selected. The sulphur atom bearing the *p*-methoxybenzyl group was used as a building block for the penam system. The other one, carrying a methyl group, served as a latent functionality to be converted into a leaving group prior to cyclization.† On treatment of non-symmetrical dialkyl sulphides with an equivalent amount of chlorine, the chlorosulphonium salt which is formed usually undergoes a unimolecular breakage of the bond between the sulphur atom and the alkyl group which has the greater ability to stabilize a positive charge.[10] It was therefore anticipated that controlled chlorinolysis of the β-lactams (4) and (7) will result in the preferential cleavage of bonds *a* and *c*, leaving bonds *b* and *d* intact. Indeed, treatment of lactams (4) and (7) with two equivalents of chlorine at 0 °C afforded the dichloro-compounds (5) * and (8)* respectively. In accordance with the postulated S_N1 mechanism, each of these compounds was obtained as mixture of two 4-chloro-epimers.

Kukolja [11] has reported the formation of similar compounds by the chlorinolysis of 6-phthalimidopenicillanates. The dichlorolactams were subsequently converted into mixtures of the starting penicillanates and their 5-epimers by treatment with tin(II) chloride.[12] This reagent has been used also in the present work, but milder conditions were employed to avoid undesired reactions involving the azido-group. Thus, treatment of the dichlorolactam (5) with one equivalent of anhydrous tin(II) chloride in dioxan at room temperature afforded benzyl (±)-6-azido-6-*epi*-penicillanate (6), while reductive cyclization of (8) gave a mixture of benzyl (±)-6-azido-5-*epi*-penicillanate (9) * and benzyl (±)-6-azidopenicillanate (10).*

Compound (6) is identical in its i.r., n.m.r., and mass spectra to the reported benzyl 6β-azidopenicillanate synthesized by a different route and subsequently converted into penicillin G.[4]

EXPERIMENTAL

For general procedures, see Part 4.[1] Reactions were conducted under argon, in dry solvents. Mass spectra were determined on an MAT 731 high resolution machine.

N-Thioformyl-3-(p-methoxybenzylthio)valine Benzyl Ester (2).—*N*-Thioformyl-3-(*p*-methoxybenzylthio)valine dicyclohexylammonium salt (1) [9] (9.88 g) and benzyl bromide (3.42 g) in dry dimethylformamide (200 ml) were stirred at 80 °C for 105 min, and then cooled to room temperature. The mixture was diluted with ethyl acetate (200 ml), filtered, evaporated, dissolved in benzene, and filtered and evaporated again. The residue was chromatographed over a silica gel column (350 g) using methylene dichloride as eluant to give, after crystallization (methylene dichloride–hexane), the *ester* (2) (4.7 g, 58%), m.p. 94—96 °C, $\nu_{max.}$ ($CHCl_3$) 1 735 and 1 610 cm^{-1}; δ($CDCl_3$) 1.37 (s) and 1.42 (s) (6 H, CMe_2), 3.67 (2 H, s, SCH_2), 3.77 (3 H, s, OMe), 5.23 (2 H, s, OCH_2), 5.35 (1 H, d, *J* 6 Hz, NHC*H*CO_2), 6.83 (2 H, d, *J* 8.5 Hz, Ar-H), 7.22 (2 H, d, *J* 8.5 Hz, Ar-H), 7.40 (5 H, s, Ph), 8.33 br (1 H, NH), and 9.58 (1 H, d, *J* 6 Hz, HCS) (Found: C, 62.7; H, 6.4; N, 3.5; S, 16.25. $C_{21}H_{25}NO_3S_2$ requires C, 62.5; H, 6.25; N, 3.5; S, 15.9%).

3-Azido-1-(1-benzyloxycarbonyl-2-methoxybenzylthio-2-methylpropyl)-4-methylthioazetidin-2-ones (4) *and* (7).—A mixture of the thioformamide (2) (2.42 g) and potassium carbonate (1.04 g) in dry acetone (36 ml) was stirred for 30 min. Methyl iodide (2.13 g) was added and stirring continued for an additional 24 h and then filtered and evaporated. The residue was dissolved in methylene dichloride, filtered, and evaporated to give the thioformimidate (3); $\nu_{max.}$ ($CHCl_3$) 1 730, 1 655, and 1 595 cm^{-1}; δ($CDCl_3$) 1.23 (s) and 1.42 (s) (6 H, CMe_2), 2.38 (3 H, s, Me), 3.73 (5 H, apparent s, SCH_2 and OMe), 4.07 (1 H, s, NCH-CO_2), 5.20 (2 H, s, OCH_2), 6.81 (2 H, d, *J* 8.5 Hz, Ar-H), 7.21 (2 H, d, *J* 8.5 Hz, Ar-H), 7.37 (5 H, s, Ph), 8.28 (1 H, s, N=CH–S). The crude thioformimidate was dissolved in dry toluene (150 ml) under argon and triethylamine (1.21 g) was added. A solution of azidoacetyl chloride (0.97 g) in dry toluene (75 ml) was added under argon, during 3 h with stirring. A second portion of triethylamine (1.21 g) was then added to the reaction mixture followed by the portionwise (3 h) addition of more azidoacetyl chloride (0.97 g) in toluene (75 ml). After stirring for an additional 15 h the mixture was filtered through Celite and evaporated. The residue was treated with azidoacetyl chloride and triethylamine as described above. This process was then repeated for a third time and the reaction product was chromatographed on a silica gel column using methylene dichloride as eluant. The fractions containing β-lactams were combined and chromatographed on a Florisil column using methylene dichloride–hexane as eluant to give the β-lactam (7) (975 mg, 32%); $\nu_{max.}$ ($CHCl_3$) 2 110, 1 765, 1 735, and 1 600 cm^{-1}; δ($CDCl_3$) 1.52 (s) and 1.57 (s) (6 H, CMe_2), 2.08 (3 H, s, SMe), 3.78 (5 H, apparent s, SCH_2 and

* All chiral compounds in this work consist of racemic mixtures; for simplicity, only one enantiomer of each pair has been displayed in the formulae.

† Opposite roles have been assigned to the sulphide grouping in the synthesis of a cepham derivative from a 4-tritylthio-β-lactam built on the nitrogen atom of methionine. See ref. 1.

OMe), 4.55 (1 H, s, $NCHCO_2$), 4.57 (1 H, d, *J* 2 Hz, β-lactam-H), 4.83 (1 H, d, *J* 2 Hz, β-lactam-H), 5.25 (2 H, s, OCH_2), 6.86 (2 H, d, *J* 9 Hz, Ar-H), 7.29 (2 H, d, *J* 9 Hz, Ar-H), 7.42 (5 H, s, Ph) (Found: $M^+ - N_3$, 458.144 3. $C_{24}H_{28}NO_4S_2$ requires $M - N_3$, 458.145 3); *m/e* 349.130 7 ($M^+ - C_8H_7OS$), 348.122 7 ($M^+ - C_8H_8OS$), 347.117 8 ($M^+ - C_8H_9OS$), 195.084 1 ($C_{11}H_{15}OS^+$), 153.036 4 ($C_8H_9OS^+$), 152.028 9 ($C_8H_8OS^+$), 151.019 3 ($C_8H_7OS^+$), 122.069 6 ($C_8H_{10}O^+$), 101.004 1 ($C_4H_5OS^+$), 91.053 8 ($C_7H_7^+$), 87.012 8 ($C_3H_5NS^+$) and 77.035 7 ($C_6H_5^+$), followed by the β-lactam (4) (514 mg 18%); $\nu_{max.}$ ($CHCl_3$) 2 110, 1 770, 1 740, and 1 605 cm^{-1}; δ($CDCl_3$) 1.53 (s) and 1.60 (s) (6 H, CMe_2), 1.90 (3 H, s, SMe), 3.77 (5 H, apparent s, SCH_2 and OMe), 4.15 (1 H, s, $NCHCO_2$), 4.48 (1 H, d, *J* 2 Hz, β-lactam-H), 4.88 (1 H, d, *J* 2 Hz, β-lactam-H), 5.22 (2 H, s, OCH_2), 6.86 (2 H, d, *J* 9 Hz, Ar-H), 7.27 (2 H, d, *J* 9 Hz, Ar-H), and 7.40 (5 H, s, Ph) (Found: $M^+ - N_2$, 472.144 4. $C_{24}H_{28}N_2O_4S_2$ requires $M - N_2$, 472.148 4); *m/e* 472.164 5 ($M^+ - CO$), 458.148 0 ($M^+ - N_3$), 349.130 6 ($M^+ - C_8H_7OS$), 348.126 2 ($M^+ - C_8H_8OS$), 320.118 0 ($C_{16}H_{20}N_2O_3S^+$), 306.113 8 ($C_{16}H_{20}NO_3S^+$), 294.080 6 ($C_{14}H_{16}NO_4S^+$), 195.083 4 ($C_{11}H_{15}OS^+$), 153.037 6 ($C_8H_9OS^+$), 152.028 6 ($C_8H_8OS^+$), 151.021 3 ($C_8H_7OS^+$), 122.069 0 ($C_8H_{10}O^+$), 101.007 6 ($C_4H_5OS^+$), 91.053 4 ($C_7H_7^+$), 87.012 3 ($C_3H_5NS^+$), and 77.035 8 ($C_6H_5^+$).

(3SR,5RS,6SR)-6-*Azido*-3-*benzyloxycarbonyl*-2,2-*dimethylpenam* (6).—The β-lactam (4) (148 mg) was dissolved in dry methylene dichloride (6 ml), under argon, at 0 °C. A solution of chlorine in carbon tetrachloride (7.5 ml, 0.094 mol) was added with stirring during 20 min. The solution was kept for an additional 15 min at 0 °C and then evaporated under reduced pressure to give the dichloro-lactam (5). The crude compound was dissolved in dry dioxan (6 ml), under argon. Anhydrous tin(II)chloride (57 mg) was added and the mixture was stirred for 26 h at room temperature. It was then filtered through a short silica gel column which was eluted with chloroform. The residue obtained after evaporation was chromatographed on a silica gel column using methylene dichloride–hexane as eluant followed by silica gel t.l.c. using methylene dichloride as eluant to give the 6-*epi*-penicillanate (6) (17 mg, 17%); $\nu_{max.}$ (CCl_4) 2 115, 1 790, and 1 750 cm^{-1}; δ($CDCl_3$) 1.39 (s) and 1.57 (s) (6 H, CMe_2), 4.53 (1 H, s, 3-H), 4.57 (1 H, d, *J* 1.5 Hz, 6-H), 5.18 (2 H, s, OCH_2), 5.23 (1 H, d, *J*, 1.5 Hz, 5-H), 7.36 (5 H, s, Ph) (Found: $M^+ - N_2$, 304.086 2. $C_{15}H_{16}N_2O_3S$ requires $M - N_2$, 304.087 8); *m/e* 213.034 7. ($M^+ - N_2 - C_7H_7$), 169.042 9 ($M^+ - N_2 - C_8H_7O_2$), 114.038 4 ($C_5H_8NS^+$), 101.003 7 ($C_2H_3N_3S^+$), 100.024 1 ($C_4H_6NS^+$), 99.045 5 ($C_5H_7O_2^+$), 91.054 4 ($C_7H_7^+$), 75.025 3 ($C_3H_7S^+$), 72.997 4 ($C_2H_3NS^+$), and 55.001 6 (C_2HNO^+) [lit.,[4] $\nu_{max.}$ (CCl_4), 2 114, 1 789, and 1 751; δ($CDCl_3$) 1.37 (s) and 1.53 (s) (*gem*-dimethyl), 4.53 (s, 3-H), 4.59 (d, *J* 1.5 Hz, 6-H), 5.18 (s, OCH_2), 5.21 (d, *J* 1.5 Hz, 5-H) and 7.39 (s, Ph); *m/e* 304 ($M^+ - N_2$)].

(3SR,5SR,6RS)-6-*Azido*-3-*benzyloxycarbonyl*-2,2-*dimethylpenam* (9) *and* (3SR,5RS,6RS)-6-*Azido*-3-*benzyloxycarbonyl*-2,2-*dimethylpenam* (10).—The β-lactam (7) (307 mg) was treated with chlorine followed by tin(II) chloride as described above for the β-lactam (4) to give, after the same work-up and chromatography, the 5-*epi*-penicillanate (9) (82 mg, 40%); $\nu_{max.}$ ($CHCl_3$) 2 115, 1 785, and 1 740 cm^{-1}; δ($CDCl_3$) 1.37 (s) and 1.60 (s) (6 H, CMe_2), 3.78 (1 H, s, $NCHCO_2$), 4.68 (1 H, d, *J* 2 Hz, β-lactam-H), 4.98 (1 H, d, *J* 2 Hz, β-lactam-H), 5.18 (2 H, s, OCH_2), and 7.36 (5 H, s, Ph) (Found: $M^+ - N_2$ 304.092 8. $C_{15}H_{16}N_2O_3S$ requires $M - N_2$, 304.087 8); *m/e* 213.032 7 ($M^+ - N_2 - C_7H_7$), 169.045 5 ($M^+ - N_2 - C_8H_7O_2$), 114.037 6 ($C_5H_8NS^+$), 101.003 6 ($C_2H_3N_3S^+$), 100.023 4 ($C_4H_6NS^+$), 91.055 5 ($C_7H_7^+$), and 75.025 7 ($C_3H_7S^+$), and the penicillanate (10) (8 mg, 4%); $\nu_{max.}$ ($CHCl_3$) 2 110, 1 785, and 1 740 cm^{-1}; δ($CDCl_3$) 1.41 (s) and 1.64 (s) (6 H, CMe_2), 4.50 (1 H, s, $NCHCO_2$), 4.90 (1 H, d, *J* 4 Hz, β-lactam-H), 5.21 (2 H, s, OCH_2), 5.46 (1 H, d, *J* 4 Hz, β-lactam-H), and 7.36 (5 H, s, Ph).

We thank Dr. Z. V. I. Zaretskii for the high-resolution mass spectra.

[8/1131 *Received*, 19*th June*, 1978]

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