One-Step Preparation of D-Penicillamine from Benzylpenicillin

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The preparation of D-penicillamine (5) was achieved by a single-step reaction of benzylpenicillin potassium salt (1) with arylamines (2, 7, and 13). The intermediates in these reactions should be the penicilloic acid α-amides. The structures of by-products formed in these reactions were also determined.

Keywords D-penicillamine; benzylpenicillin; benzylpenicilloic acid α-amide; arylamine; ring fission

D-Penicillamine (**5**) has been clinically used to treat cystinuria, Wilson's disease and rheumatoid disease.[1] Various methods for the preparation of **5** from benzylpenicillin have been reported.[2] In the previous paper,[3] we reported that **5** was easily obtained by the reaction of benzylpenicilloic acid α-amides, prepared by aminolysis of benzylpenicillin, with arylamines such as *o*-phenylenediamine (**13**), *o*-aminothiophenol (**7**) and anilines (**2a** and **2b**) through ring cleavage of the thiazolidine ring. During further studies to develop a convenient method for the preparation of **5**, we found that **5** can be easily obtained in a single step from benzylpenicillin upon treatment with arylamines such as **2a**, **2b**, **7**, and **13**. The results of our studies are presented here.

First, we examined the reaction of benzylpenicillin potassium salt (**1**) with aniline (**2a**) and *p*-toluidine (**2b**). Compound **1** was heated with 4 eq of **2a** in a mixture of water, toluene and acetic acid under reflux to give **5** in 41% yield, accompanied with a 40% yield of the acrylamide **6a**. When **2b** was used instead of **2a**, **5** and **6b** were obtained in 71% and 95% yields. The pathway for the formation of **5** and **6** is postulated to be as shown in Chart 1.

It seems likely that the reaction involves nucleophilic cleavage of the β-lactam ring by the arylamine at the first stage[4] and the subsequent ring fission of the thiazolidine ring of the intermediate **3** by **2** then gives **5** and the Schiff base intermediate **4**. Apparently **4** should be easily convertible to **6** through tautomerization.

The geometry of the double bond of **6** was determined as *Z*, based on the chemical shifts of the amino proton in the proton nuclear magnetic resonance (^{1}H-NMR) spectra.[3] The amino proton (=CH−NHPh) signals in *E* isomers[5] were observed at lower field than those in the corresponding *Z* isomers on account of the hydrogen bond between the amino proton and carbonyl oxygen (PhNHCO–). The ^{1}H-NMR spectra of **6a**, **b** showed a doublet signal due to NH at 8.32 (J=12 Hz) and 8.19 (J=12 Hz), while the *E* isomers showed NH signals at 10.45 (J=12 Hz) and 10.39 (J=12 Hz).

We then examined the reaction of **1** with arylamines, which have nucleophilic groups such as amino or mercapto at the *ortho* position. The reaction of **1** with *o*-aminothiophenol (**7**) afforded **5** in 68% yield accompanied with formation of the 2-substituted benzothiazole **11** and benzothiazole (**12**)[3] in 60% and 51% yields, respectively.

It seems likely that the reaction proceeds through the same Schiff base intermediate **9** as is formed in the reaction of **1** with **2**. However, in this case, **9** undergoes intramolecular cyclization to give the benzothiazole derivative **10** as the intermediate, which undergoes further C–C bond cleavage between the 2- and α-position of **10** by protonation at nitrogen on the benzothiazole ring to yield **11** and **12**, as shown in Chart 2.

The reaction of **1** with **13** gave a rather complicated result. Though **5** was also obtained in 51% yield in this reaction, the 2-substituted benzimidazole **15**[6] (45% yield), the benzimidazole (**16**)[3] (41% yield), the amide **21** (2% yield), the benzimidazolinone **18** (4% yield), and the 2-benzylbenzimidazole (**22**)[7] (15% yield) were obtained in

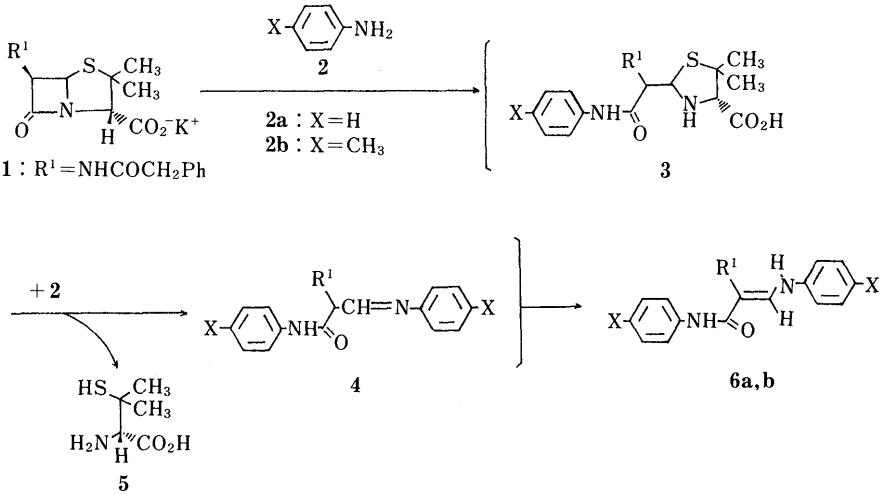

Chart 1

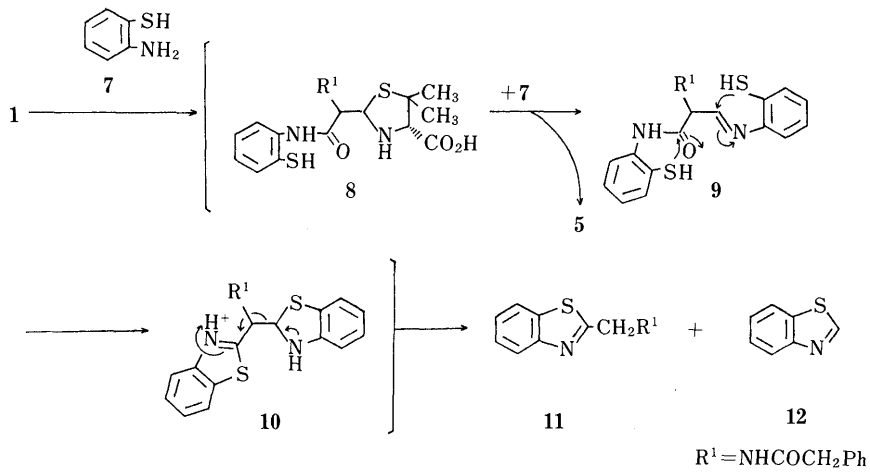

Chart 2

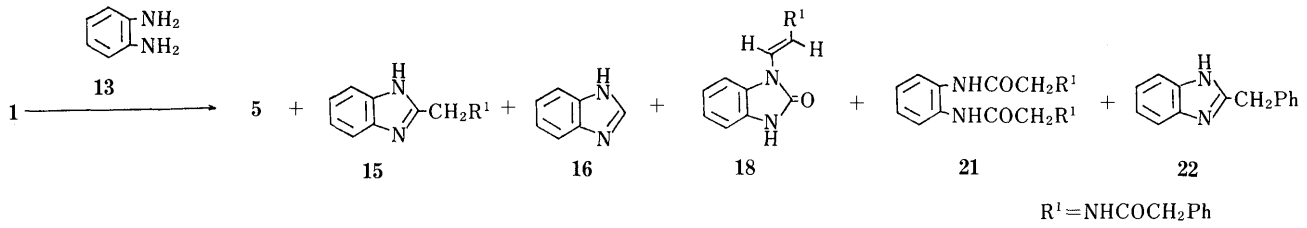

Chart 3

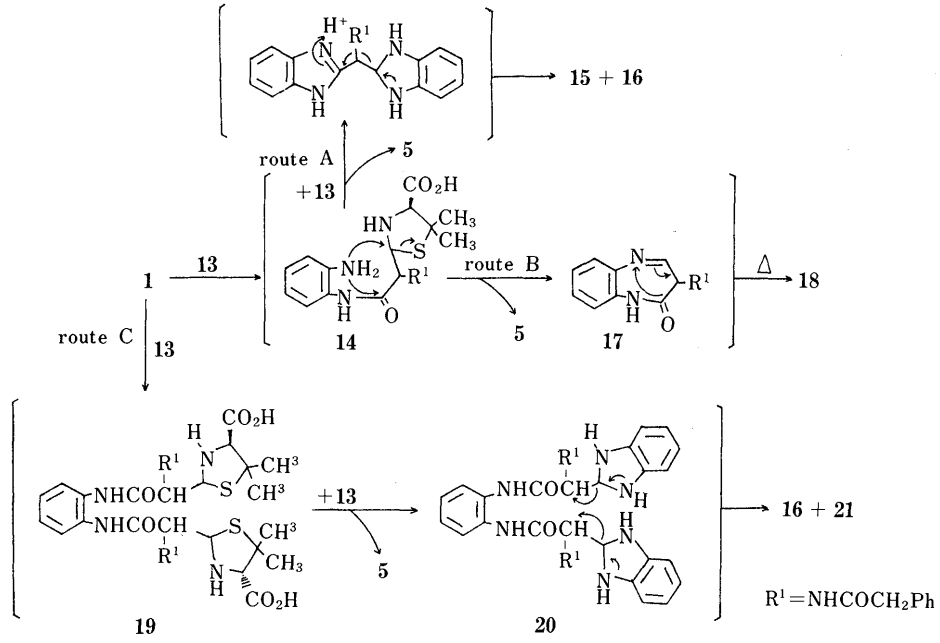

Chart 4

addition to **5**. The structures of these products were supported by their spectral data.

As plausible pathways for the formation of these products, three routes (route A, route B, and route C) can be considered (Chart 4). Route A: Formation of **5**, **15**, and **16** can be accounted for a process similar to that of formation of **5**, **11** and **12** upon treatment of **1** with **7**. Route B: Compound **18** is obtained through the benzodiazepine intermediate **17** formed by the intramolecular cyclization of **14** with liberation of **5**. The intermediate **17** undergoes a molecular rearrangement similar to that reported by Israel *et al.*[8] to give **18**. Route C: After reaction of **13** with 2 mol of **1**, thiazolidine ring fission reaction by another molecule of **13** occurs *via* the intermediate **19** to give **5** and the benzothiazolidine intermediate **20**. Then, the C–C bond between the 2- and α-position of **20** is cleaved with participation of the lone pair of the nitrogen atom, and two products, **16** and **21**, are formed. The phenylacetyl group in R^1 is also attacked by the nucleophile **13** to give **22**.

In conclusion, ring fission of **1** with aniline (**2a**), *p*-tolu-

idine (**2b**) and *o*-aminothiophenol (**7**) proceeded smoothly and a one-step synthesis of **5** was achieved. Among the arylamines used in this study, **2b** gave the best results with regard to the yield of **5**. However, the same reaction with *o*-phenylenediamine (**13**) gave rather complicated results.

Experimental

All melting points are uncorrected. Mass spectra (MS) were taken on a Shimadzu LKB 9000 spectrometer, and infrared (IR) spectra were recorded on a JASCO DS-301 spectrometer. ^{1}H-NMR spectra were taken on Varian XL-200 (200 MHz) and Hitachi-Perkin-Elmer R-20 (60 MHz) spectrometers with tetramethylsilane as an internal standard. Chemical shifts are given in δ (ppm) values.

Reaction of Benzylpenicillin Potassium Salt (1) with *p*-Toluidine (2b) **1** (3.72 g, 10 mmol) and **2b** (4.29 g, 40 mmol) were added to a mixture of water (20 ml), toluene (20 ml), and acetic acid (4.8 g, 80 mmol). The mixture was heated under reflux with stirring for 4 h under a nitrogen atmosphere. After standing of the resulting mixture at room temperature for 1 h, the precipitated product was filtered off, washed with water, and then dried *in vacuo*. Recrystallization from methanol gave (*Z*)-*N*-(*p*-methylphenyl)-3-(*p*-methylanilino)-2-(2-phenylacetamido)acrylamide (**6b**) (3.79 g, 95%), mp 185—187 °C. IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O), 3000, 3180 (NH). ^{1}H-NMR (DMSO-d_6) δ: 2.22 (6H, s, 2×CH_3), 3.71 (2H, s, CH_2Ph), 6.98—7.50 (13H, m, ArH), 7.75 (1H, d, J=12 Hz, >=<NH), 8.19 (1H, d, J=12 Hz, >=<NH), 8.67 (1H, s, NH), 8.92 (1H, s, NH). MS *m/z*: 399 (M^+). *Anal.* Calcd for $C_{25}H_{25}N_3O_2$: C, 75.16; H, 6.31; N, 10.52. Found: C, 75.02; H, 6.19; N, 10.75.

The organic layer was removed from the filtrate. Subsequently, the aqueous layer was washed with chloroform (10 ml) and evaporated under reduced pressure. The resulting residue was triturate with methanol. The separated crystals were collected by filtration, washed with methanol, and dried to give D-penicillamine (**5**) (848 mg, 57%), mp 201—202 °C, (lit.[9] mp 200—205 °C), $[\alpha]_D^{20}$ −63.20° (1N NaOH, c=1), (lit.[9] $[\alpha]_D^{22}$ −61°). ^{1}H-NMR (60 MHz, CF_3CO_2H) δ: 1.65 (3H, s, CH_3), 1.81 (3H, s, CH_3), 2.26 (1H, br s, SH), 4.30 (1H, m, methine proton), 7.60 (2H, br s, NH_2). *Anal.* Calcd for $C_5H_{11}NO_2S$: C, 40.24; H, 7.43. Found: C, 40.21; H, 7.39.

The filtrate was acidified by the addition of concentrated hydrochloric acid (1.67 ml, 20 mmol) under ice cooling. Insoluble material was filtered off. The filtrate was treated with triethylamine (1.01 g, 10 mmol), and the precipitated solid was collected by filtration and washed with methanol to give **5** (213 mg). Total yield was 71%.

Compound **1** was also treated with **2a** in the same manner to give **5** and **6a** in 41% and 40% yields. Compound **5**: mp 203—205 °C, $[\alpha]_D^{22}$ −63.80° (1N NaOH, c=1). Compound **6a**: mp 198—199 °C, IR ν_{max}^{KBr} cm^{-1}: 1672 (C=O), 3030, 3220 (NH). ^{1}H-NMR (DMSO-d_6) δ: 3.74 (2H, s, -CH_2Ph), 6.93—7.61 (15H, m, ArH), 7.79 (1H, d, J=12 Hz, >=<NH), 8.32 (1H, d, J=12 Hz, >=<NH), 8.84 (1H, s, NH), 8.98 (1H, s, NH). MS *m/z*: 371 (M^+). *Anal.* Calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.24; H, 5.74; N, 11.42.

Reaction of 1 with *o*-Aminothiophenol (7) **1** (3.72 g, 10 mmol) and **7** (2.50 g, 20 mmol) were added to a mixture of water (20 ml), toluene (20 ml), and acetic acid (2.40 g, 40 mmol). The mixture was heated under reflux with stirring for 3 h under a nitrogen atmosphere. After cooling, the organic layer was removed, and the aqueous layer was washed with three 30 ml portions of chloroform and evaporated under reduced pressure. The resulting residue was triturated with methanol. The separated crystals were collected by filtration, washed with methanol and dried to give **5** (695 mg, 47%), mp 195—198 °C, $[\alpha]_D^{20}$ −62.90° (1N NaOH, c=1).

The filtrate was acidified by the addition of concentrated hydrochloric acid (1.67 ml, 20 mmol) under ice cooling. Insoluble material was filtered off. The filtrate was treated with triethylamine (1.01 g, 10 mmol), and the precipitated solid was collected by filtration and washed with methanol to give **5** (314 mg). Total yield was 68%.

The organic extracts were washed with water, dried over sodium sulfate, and evaporated under reduced pressure. The residue was subjected to chromatography on silica gel. The chloroform eluate was purified by vacuum distillation (bp 75 °C (2 mmHg)) to give benzothiazole (**12**) (689 mg, 51%). Further elution with 2% methanol in chloroform (v/v) afforded 2-[(2-phenylacetamido)methyl]benzothiazole (**11**) (1.70 g, 60%) as a white solid, mp 107—109 °C (from methanol–petroleum ether). IR ν_{max}^{KBr} cm^{-1}: 1638 (C=O), 3270 (NH). ^{1}H-NMR ($CDCl_3$) δ: 3.69 (2H, s, CH_2Ph), 4.82 (2H, d, J=6 Hz, CH_2NH), 6.38 (1H, t, J=6 Hz, NH), 7.22—7.98 (9H, m, ArH). MS *m/z*: 282 (M^+). *Anal.* Calcd for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92. Found: C, 68.33; H, 5.17; N, 9.71.

Reaction of 1 with *o*-Phenylenediamine (13) **1** (7.45 g, 20 mmol) and **13** (4.33 g, 40 mmol) were added to a solution of acetic acid (4.80 g, 80 mmol) in water (40 ml). The mixture was heated under reflux with stirring for 8 h under a nitrogen atmosphere.

After cooling, the mixture was extracted with chloroform. The aqueous layer was evaporated and the resulting residue was triturated with methanol. The separated crystals were collected by filtration, washed with methanol, and dried to give **5** (1.51 g, 51%) as colorless crystals, mp 198—199 °C, $[\alpha]_D^{20}$ −63.50° (1N NaOH, c=1). The filtrate was evaporated under reduced pressure. The residue was subjected to chromatography on silica gel. Elution with 5% methanol in chloroform (v/v) afforded benzimidazole (**16**) (972 mg, 41%) as colorless prisms, mp 168—170 °C. The organic extract was washed with water, dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using 2—20% methanol in chloroform (v/v) as an eluent to give 2-benzylbenzimidazole (**22**) (612 mg, 15%), 2-[(2-phenylacetamido)methyl]benzimidazole (**15**) (2.40 g, 45%), (*E*)-1-[2-(2-phenylacetamido)-1-ethenyl]benzimidazolidin-2-one (**18**) (237 mg, 4%) and *N*,*N*′-bis[(2-phenylacetamido)acetyl]-*o*-phenylenediamine (**21**) (98 mg, 2%).

22: mp 183—186 °C (from ether) (lit.[7] mp 184.5—187 °C).

15: Colorless prisms, mp 185—187 °C (from benzene). Spectral data were identical with those of an authentic sample reported in our previous paper.[6]

18: Colorless prisms, mp 250—252 °C (from benzene). IR ν_{max}^{KBr} cm^{-1}: 1645 (amide C=O), 1715 (urea C=O), 3180, 3250 (NH). ^{1}H-NMR (DMSO-d_6) δ: 3.58 (2H, s, CH_2Ph), 6.78 (1H, d, J=12 Hz, olefine proton), 6.99—7.38 (9H, m, ArH), 7.45 (1H, dd, J=9 and 12 Hz, olefine proton), 10.26 (1H, d, J=9 Hz, NHCO), 11.11 (1H, s, NH). MS *m/z*: 293 (M^+). *Anal.* Calcd for: $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.55; H, 5.06; N, 14.06.

21: White solid, mp 208—211 °C (from benzene). IR ν_{max}^{KBr} cm^{-1}: 1643, 1678 (C=O), 3240 (NH). ^{1}H-NMR (DMSO-d_6) δ: 3.33 (4H, s, CH_2Ph), 3.91 (4H, d, J=6 Hz, CH_2NH), 7.36—7.65 (14H, m, ArH), 8.45 (2H, t, J=6 Hz, CH_2NH), 9.38 (2H, s, NH). MS *m/z*: 458 (M^+). *Anal.* Calcd for $C_{26}H_{26}N_4O_4$: C, 68.10; H, 5.72; N, 12.22. Found: C, 68.01; H, 5.69; N, 12.08.

References and Notes

1) J. D. Schuman and K. H. Bradley, *Science*, **169**, 595 (1970); I. A. Jaffe, *Ann. Rheum. Dis.*, **22**, 71 (1963); Y. Shiokawa, Y. Horiuchi, M. Kageyama, T. Okada and T. Azuma, *Arthritis, Rheum.*, **20**, 1464 (1977).
2) W. M. Weigert, H. Offermanns and P. Scherberich, *Angew. Chem.*, **87**, 372 (1975).
3) T. Ogawa, K. Tomisawa and K. Sota, *Chem. Pharm. Bull.*, **36**, 1957 (1988).
4) H. Hitomi, *Yakugaku Zasshi*, **73**, 428 (1953).
5) Treatment of **6a**, **b** with silica gel in metanol under reflux for 15 h gave a mixture of **6a**,**b** and their *E* isomers. The *E* isomers were isolated by chromatography on silica gel with methanol–chloroform.
6) T. Ogawa, K. Tomisawa and K. Sota, *Heterocycles*, **27**, 1421 (1988).
7) S. Tanimoto, M. Ohsone and R. Oda, *Kogyo Kagaku Zasshi*, **69**, 2015 (1966).
8) M. Israel, L. C. Jones and E. J. Modest, *Tetrahedron Lett.*, **1968**, 4811; M. Israel and L. C. Jones, *J. Heterocycl. Chem.*, **6**, 735 (1969); G. Vernin, H. Domlog, C. Siv and J. Metzger, *ibid.*, **18**, 85 (1981); O. Meth-Cohn and D. I. Smith, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 261; R. Achour, E. M. Essassi and R. Zniber, *Tetrahedron Lett.*, **29**, 195 (1988).
9) J. J. Herak, M. Kovacevic and B. Gaspert, *Croat. Chem. Acta*, **49**, 141 (1977).